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(54) Use of corticotropin releasing factor antagonists for treating syndrome X

(57) The present invention relates to compositions and methods of achieving a thereapeutic effect including, the treatment or prevention of syndrome X in an animal, preferably a mammal including a human subject or a companion animal, using a corticotropin releasing factor (CRF) antagonist alone or together with a glucocorticoid receptor antagonist.

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Description

BACKGROUND OF THE INVENTION

[0001] The present invention relates to compositions and methods of achieving a therapeutic effect, including the treatment or prevention of Syndrome X, in an animal, preferably a mammal, including a human subject, and a companion animal, using a corticotropin releasing factor (CRF) antagonist alone or together with a glucocorticoid receptor (GR) antagonist.

[0002] Syndrome X, also known as metabolic syndrome, plurimetabolic syndrome or insulin resistance syndrome, encompasses a complex of disturbances of carbohydrate and fat metabolism characterized by obesity, dyslipoproteinemia (low HDL and high LDL, VLDL and triglycerides), hyperinsulinemia, insulin resistance, glucose intolerance and hypertension (Atherosclerosis X, F.P. Woodford, J. Davignon, A. Sniderman (Eds.), Elsevier Science BV, Amsterdam (1995): 520-524.). Syndrome X is associated with an elevated risk for cardiovascular disease.

[0003] There are striking similarities between Cushing's disease and Syndrome X, both being characterized by visceral obesity, hypertension, insulin resistance, glucose intolerance and hyperlipidemia (Endocrine Research, 22(4), 701-708 (1996)). Cushing's disease is caused by hypersecretion of cortisol, the most important human glucocorticoid, by the adrenal cortex. Cortisol is known to cause visceral fat accumulation and insulin resistance (Pennington Cent. Nutr. Ser. (1996), 5 (Molecular and Genetic Aspects of Obesity), 340-352; Nutrition, 13:795-803 (1997); and Prog. Obes. Res., 7:505-510 (1996)). Cortisol promotes hepatic gluconeogenesis and glycogen deposition and increases blood glucose levels. Cortisol also increases the sensitivity of adipose tissue to lipolytic hormones, elevating fatty acid levels and thereby stimulating triglyceride synthesis and VLDL (very low density lipoprotein) secretion. The VLDL is converted to VLDL remnants or LDL (low density lipoprotein) which are largely taken up by the liver via the LDL receptors, resulting in down-regulation of the LDL receptor and consequently hypertriglyceridemia and hyper-apobetalipoproteinemia. Abnormalities of glucocorticoid secretion and sensitivity in men have been shown to be associated with hypertension and insulin resistance (Endocrine Research, 22(4), 701-708 (1996); and Hypertension, 1998;31: 891-895). Hypersecretion of cortisol is the result of excessive secretion of ACTH (adrenocorticotropic hormone). Administration of ACTH has been shown to increase blood pressure in animals (J. Hypertension, 16:593-600 (1998)). The secretion of ACTH is controlled by the releasing hormone, corticotropin releasing factor (CRF or CRH). Thus, a CRF (CRH) antagonist, by decreasing ACTH secretion, will ameliorate the hypersecretion of glucocorticoids and thereby be of therapeutic benefit in the treatment of Syndrome X.

[0004] In addition, the levels of glucocorticoids present in the body are primarily, but not solely, determined by the concentration of CRF, so the use of a combination of a CRF antagonist and a GR antagonist will be of greater therapeutic benefit in the treatment of Syndrome X than the use of a CRF antagonist alone.

[0005] International Patent Application Publication No. WO 97/25042, published 17 July 1997, discloses methods for the treatment and/or prophylaxis of Syndrome X by the administration of an agonist of PPARα and PPARγ, or a pharmaceutically acceptable derivative thereof, to a human or non-human animal in need of such treatment.

[0006] International Patent Application Publication No. WO 99/17761, published 15 April 1999, discloses the use of nordihydroguaiaretic acid to treat or ameliorate the characteristic manifestations of Syndrome X in a non-diabetic animal with normal serum glucose levels.

[0007] CRF antagonists are disclosed in U.S. Patents 4,605,642 and 5,063,245. They are also disclosed in International patent publications WO 95/33750; WO 95/34563; WO 94/13661; WO 94/13644; WO 94/13643; WO 94/13676; WO 94/13677; WO 95/33727; WO 98/05661; WO 98/08847; WO 98/08846; and European patent publications EP 778277 and EP 773023. CRF antagonists are also disclosed in the following patent publications: EP 576350; EP 659747; EP 812831; WO 95/10506; WO 96/35689; WO 96/39400; WO 97/00868; WO 97/14684; WO 97/29109; WO 97/29110; WO 97/35539; WO 97/35580; WO 97/35846; WO 97/44038; WO 97/45421; WO 98/03510; WO 98/08821; WO 98/11075; WO 98/15543; WO 98/21200; WO 98/27066; WO 98/29397; WO 98/29413; WO 98/42699; WO 98/35967; WO 98/42706; WO 98/45295; WO 98/47874; WO 98/47903; WO 98/51312; WO 99/01454; WO 99/01439; WO 99/10350; WO 99/12908; WO 99/00373; WO 99/38868; WO 99/51597; WO 99/51599; WO 99/40089; WO 99/51598; and WO 99/51600. They are also disclosed in United States Patents 5,109,111; 5,132,111; 5,245,009; 5,464,847; 5,493,006; 5,510,458; 5,644,057; 5,663,292; 5,668,145; 5,705,646; 5,712,303; and 5,723,608. An overview of the patent literature on CRF antagonists is provided in T.E. Christos and A. Arvanitis, Exp. Opin. Ther. Patents (1998) 8(2):143-152.

[0008] The importance of CRF antagonists is set out in the literature, e.g., P. Black, Scientific American: "Science & Medicine," 1995, 2:16-25; T. Lovenberg, et al., Current Pharmaceutical Design, 1995, 1: 305-316; D.T. Chalmers et al., Trends in Pharmacological Sciences, April 1996, pages 166-172; and United States Patent 5,063,245. An outline of the activities possessed by CRF antagonists is found in M. J. Owens et al., 1991, Pharm. Rev., 43:425-473. CRF antagonists are described in the art as being effective in the treatment of stress-related illnesses, mood disorders such as depression, major depressive disorder, single episode depression, recurrent depression, child abuse induced de-

pression, postpartum depression, dysthemia, bipolar disorders, and cyclothymia; chronic fatigue syndrome; eating disorders such as anorexia and bulimia nervosa; generalized anxiety disorder; panic disorder; phobias; obsessive-compulsive disorder; post-traumatic stress disorder; pain perception such as fibromyalgia; headache; gastrointestinal diseases; hemorrhagic stress; ulcers; stress-induced psychotic episodes; fever; diarrhea; post-operative ileus; colonic hypersensitivity; irritable bowel syndrome; Crohn's disease; spastic colon; inflammatory disorders such as rheumatoid arthritis and osteoarthritis; pain; asthma; psoriasis; allergies; osteoporosis; premature birth; hypertension, congestive heart failure; sleep disorders; neurodegenerative diseases such as Alzheimer's disease, senile dementia of the Alzheimer's type, multiinfarct dementia, Parkinson's disease, and Huntington's disease; head trauma; ischemic neuronal damage; excitotoxic neuronal damage; epilepsy; stroke; spinal cord trauma; psychosocial dwarfism; euthyroid sick syndrome; syndrome of inappropriate antidiuretic hormone; obesity; chemical dependencies and addictions; drug and alcohol withdrawal symptoms; infertility; cancer; muscular spasms; urinary incontinence; hypoglycemia and immune dysfunctions including stress induced immune dysfunctions, immune suppression and human immunodeficiency virus infections; and stress-induced infections in humans and animals.

[0009] GR antagonists are disclosed in the following references: International patent application PCT/IB00/00366, filed 27 March 2000, and assigned to the assignee hereof; International patent publications WO 99/41256 and WO 99/41257; U.S. Patent 5,696,127; European patent publication 188396; European patent publication 683172; International patent publication WO 98/26783; International patent publication WO 98/27986; International patent publication WO 98/31702; European patent publication 903146; and International patent publications WO 99/41256 and WO 99/41257.

[0010] GR modulators (e.g., agonists, partial agonists, antagonists and partial antagonists) can be used in the treatment of diseases associated with an excess or a deficiency of glucocorticoids in the body. As such, they may be used to treat the following: obesity, diabetes, cardiovascular disease, hypertension, Syndrome X, depression, anxiety, glaucoma, human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS), neurodegeneration (for example, Alzheimer's and Parkinson's), cognition enhancement, Cushing's Syndrome, Addison's Disease, osteoporosis, frailty, inflammatory diseases (such as osteoarthritis, rheumatoid arthritis, asthma and rhinitis), tests of adrenal function, viral infection, immunodeficiency immunomodulation, autoimmune diseases, allergies, wound healing, compulsive behavior, multi-drug resistance, addiction, psychosis, anorexia, cachexia, post-traumatic stress syndrome, post-surgical bone fracture, medical catabolism and prevention of muscle frailty.

[0011] All of the hereinabove and below cited U.S. patents, U.S. and PCT international patent applications, published European patent applications and published PCT international patent applications are incorporated herein by reference in their entirety.

SUMMARY OF THE INVENTION

[0012] The present invention provides methods of treating or preventing Syndrome X in an animal which comprises administering to said animal an amount of a corticotropin releasing factor antagonist. More particularly, the present invention provides these methods wherein a therapeutically effective amount of a corticotropin releasing factor antagonist is administered. More particularly, the present invention provides these methods wherein the corticotropin releasing factor antagonist is a compound of a particular generic formula as described below.

[0013] Also, the present invention provides methods of treating or preventing Syndrome X in an animal which comprises administering to said animal an amount of a corticotropin releasing factor antagonist and an amount of a glucocorticoid receptor antagonist; wherein the amount of the corticotropin releasing factor antagonist and the amount of the glucocorticoid receptor antagonist result in a therapeutic effect. More particularly, the present invention provides these methods wherein the corticotrophin releasing factor antagonist is a compound of a particular generic formula as described below. More particularly, the present invention provides these methods wherein the glucocorticoid receptor antagonist is a compound of formula IA wherein the variables are as defined below.

[0014] Also, the present invention provides pharmaceutical compositions for treating or preventing Syndrome X which comprises an amount of a corticotropin releasing factor antagonist and a pharmaceutically acceptable vehicle, carrier or diluent. More particularly, the present invention provides these compositions which comprise a therapeutically effective amount of a corticotropin releasing factor antagonist. More particularly, the present invention provides these compositions wherein the corticotropin releasing factor is a compound of a particular generic formula as described below.

[0015] Also, the present invention provides pharmaceutical compositions for treating or preventing Syndrome X which comprises an amount of a corticotropin releasing factor antagonist, an amount of a glucocorticoid receptor antagonist and a pharmaceutically acceptable vehicle, carrier or diluent; wherein the amount of the corticotropin releasing factor antagonist and the amount of the glucocorticoid receptor antagonist result in a therapeutic effect. More particularly, the present invention provides these compositions wherein the corticotrophin releasing factor antagonist is a compound of a particular generic formula as described below. More particularly, the present invention provides these compositions

wherein the glucocorticoid receptor antagonist is a compound of formula IA wherein the variables are as defined below.

[0016] Also, the present invention provides kits which comprise an amount of a corticotropin releasing factor antagonist and a pharmaceutically acceptable vehicle, carrier or diluent in a first unit dosage form; an amount of a glucocorticoid receptor antagonist and a pharmaceutically acceptable vehicle, carrier or diluent in a second unit dosage form; and a container for containing said first and second dosage forms; wherein the amount of the corticotropin releasing factor antagonist and the amount of the glucocorticoid receptor antagonist result in a therapeutic effect. More particularly, the present invention provides these kits wherein the corticotrophin releasing factor antagonist is a compound of a particular generic formula as described below. More particularly, the present invention provides these kits wherein the glucocorticoid receptor antagonist is a compound of formula IA wherein the variables are as defined below.

[0017] The present invention relates to compositions and methods useful in achieving therapeutic effects, such as the treatment or prevention of Syndrome X, which compositions preferably comprise a corticotropin releasing factor (CRF) antagonist alone or in combination with a glucocorticoid receptor (GR) antagonist, and a pharmaceutically acceptable carrier, vehicle or diluent, and which methods preferably comprise administering to an animal, preferably a mammal including a human subject or a companion mammal in need of such treatment, a CRF antagonist and a GR antagonist.

[0018] The terms "treating" and "treatment," as used herein, unless otherwise indicated, include, inter alia, palliative and curative treatment of any disorder enumerated within the methods of the present invention.

[0019] The terms "preventing," "prevention" and "prophylaxis," as used herein, unless otherwise indicated, include the inhibition or preclusion of the development of any disorder enumerated within the methods of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0020] Syndrome X is the syndrome characterized by an initial insulin resistant state, generating hyperinsulinaemia, dyslipidaemia and impaired glucose tolerance, which can progress to non-insulin dependent diabetes mellitus (Type II diabetes), characterized by hyperglycaemia and which then further progresses to diabetic complications.

[0021] CRF antagonists alone or together with GR antagonists are effective for the treatment and/or prophylaxis of Syndrome X and the resulting complications thereof. These compounds are therefore considered to be useful for the treatment and/or prophylaxis of any combination of the following list of disorders associated with Syndrome X and the resulting complications thereof, including, for example, insulin resistance, diabetes, more particularly non-insulin dependent diabetes mellitus (Type II diabetes), and the complications associated with diabetes, dyslipidaemia, hyperinsulinaemia, hyperglycaemia, atherosclerosis, hypertension, cardiovascular disease and obesity. This list is for purposes of illustration only and is not intended to limit the scope of the present invention.

[0022] The complications associated with diabetes include, for example, cardiovascular disease, especially atherosclerosis, retinopathy, neuropathy and renal disease including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

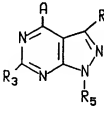
[0023] The term corticotropin releasing factor (CRF) antagonist refers to a compound having the ability to inhibit or reverse the deleterious effects of the presence of CRF. It is well known that CRF profoundly stimulates the pituitary-adrenalcortical axis and, in dysfunctional states, initiates behavioral, physiological and endocrine responses that are essentially identical to those observed when animals, including humans and companion animals, are subjected to a stressful environment. Therefore, CRF antagonists are known to have utility, inter alia, in the amelioration of certain stress-induced conditions including memory loss, mood alteration, depression, hypertension and the like.

[0024] Any CRF antagonist can be used to practice the present invention, including those that are described in U. S. Patents 4,605,642 and 5,063,245; International patent publications WO 95/33750; WO 95/34563; WO 94/13661; WO 94/13644; WO 94/13643; WO 94/13676; W094/13677; WO 95/33727; WO 98/05661; WO 98/08847; and WO 98/08846; and European patent publications EP 778277; and EP 773023. They also include those of the following patent publications: EP 576350; EP 659747; EP 812831; WO 95/10506; WO 96/35689; WO 96/39400; WO 97/00868; WO 97/14684; WO 97/29109; WO 97/29110; WO 97/35539; WO 97/35580; WO 97/35846; WO 97/44038; WO 97/45421; WO 98/03510; WO 98/08821; WO 98/11075; WO 98/15543; WO 98/21200; WO 98/27066; WO 98/29397; WO 98/29413; WO 98/42699; WO 98/35967; WO 98/42706; WO 98/45295; WO 98/47874; WO 98/47903; WO 98/51312; WO 99/01454; W099/01439; W099/10350; W099/12908; W099/00373; WO 99/38868; WO 99/51597; WO 99/51599; WO 99/40089; WO 99/51598; and WO 99/51600. They are also disclosed in United States Patents 5,109,111; 5,132,111; 5,245,009; 5,464,847; 5,493,006; 5,510,458; 5,644,057; 5,663,292; 5,668,145; 5,705,646; 5,712,303; and 5,723,608. Additional information relating to preparing certain of these compounds is provided in WO 96/39388, which describes the production of certain intermediates. As noted above, the texts of all of these publications are incorporated by reference herein in their entireties.

[0025] Following are listed particular examples of CRF antagonists that may be used in practicing the invention. It is understood that in the generic formulae employed below, the variables employed, e.g., "A", "B", "R_1", "R_2", etc. have the meanings attributed to them only in the particular Roman numeral section in which they are found. Thus, the

meaning attributed, for example, to "R^1" is different for the structures in section I and the structures of the other sections.

I. For example, the CRF antagonist may be of the following formula, described in WO 94/13677:



and the pharmaceutically acceptable acid addition salts thereof, wherein A is NR_1R_2, $CR_1R_2R_{11}$, or C (=CR_1R_{12})R_2, $NHCR_1R_2R_{11}$, $OCR_1R_2R_{11}$, $SCR_1R_2R_{11}$, $NHNR_1R_2$, $CR_2R_{11}NHR_1$, $CR_2R_{11}OR_1$, $CR_2R_{11}SR_1$ or $C(O)R_2$;

R_1 is hydrogen, or C_1-C_6 alkyl which may be substituted by one or two substituents R_6 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, O-C(O)-(C_1-C_6 alkyl), O-C(O)-N(C_1-C_4 alkyl)(C_1-C_2 alkyl); amino, NH(C_1-C_4 alkyl), S(C_1-C_6 alkyl), OC(O)NH(C_1-C_4alkyl), N(C_1-C_2 alkyl)C(O)(C_1-C_4 alkyl), NHC(O)(C_1-C_4 alkyl), COOH, C(O)(C_1-C_4 alkyl), C(O)NH(C_1-C_4 alkyl), C(O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, CN, NO_2, SO(C_1-C_4 alkyl); SO_2(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), and said C_1-C_5 alkyl may have one or two double or triple bonds;

R_2 is C_1-C_{12} alkyl, aryl or (C_1-C_{10} alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benziso-thiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, oxazolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or (C_1-C_6 alkylene) cycloalkyl, wherein said cycloalkyl may have one or two of O, S or N-Z, wherein Z is hydrogen, substituted , independently, for one or two carbons of said cycloalkyl, C_1-C_4 alkyl, benzyl or C_1-C_4 alkanoyl, wherein R^2 may be substituted independently by from one to three of chloro, fluoro, or C_1-C_4 alkyl, or one of hydroxy, bromo, iodo, C_1-C_6 alkoxy, OC(O)(C_1-C_6 alkyl), O-C-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), S(C_1-C_6 alkyl), NH_2, NH(C_1-C_2 alkyl), N(C_1-C_4 alkyl) C(O)(C_1-C_4 alkyl), NHC(O)(C_1-C_4 alkyl), COOH, C(O)O(C_1-C_4 alkyl), C(O)NH(C_1-C_4 alkyl), C(O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, CN, NO_2, SO(C_1-C_4 alkyl), SO_2(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), and wherein said C_1-C_{12} alkyl or C_1-C_{10} alkylene may have one to three double or triple bonds; or

NR_1R_2 or $CR_1R_2R_{11}$ may form a 4- to 8-membered ring optionally having one or two double bonds or one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, benzyl, or C_1-C_4 alkanoyl;

R_3 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, O(C_1-C_6 alkyl), NH(C_1-C_6 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, S(C_1-C_4 alkyl), SO(C_1-C_4 alkyl), or SO_2(C_1-C_4 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may have one or two double or triple bonds and may be substituted by from 1 to 3 R_7 substituents independently selected from the group consisting of hydroxy, amino, C_1-C_3 alkoxy, dimethylamino, diethylamino, methylamino, ethylamino, NHC(O)CH_3, fluoro, chloro or C_1-C_3 thioalkyl;

R_4 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, amino, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_2 alkyl), SO_n(C_1-C_6 alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, carboxy, or amido, wherein said C_1-C_6 alkyls may be substituted by one to three of hydroxy, amino, carboxy, amido, NHC(O)O(C_1-C_4 alkyl), NH(C_1-C_4 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl), C(O)O(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

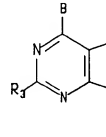
R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, piperazinyl, piperidinyl, or tetrazolyl, wherein each one of the above groups may be substituted independently by from one to three of fluoro, chloro, bromo, formyl, C_1-C_6 alkyl, C_1-C_6 alkoxy or trifluoromethyl, or one of hydroxy, iodo, cyano, nitro, amino, cyclopropyl, NH(C_1-C_4 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl), COO(C_1-C_4 alkyl); CO(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SO_2NH_2, $NHSO_2$(C_1-C_4 alkyl), S(C_1-C_6 alkyl), SO_2(C_1-C_6 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may have one double or triple bond and may be substituted by one or two of fluoro, chloro, hydroxy, amino, methylamino, dimethylamino or acetyl, with the proviso that R_5 is not unsubstituted phenyl;

R_{11} is hydrogen, hydroxy, fluoro, chloro, COO(C_1-C_2 alkyl), cyano, or CO(C_1-C_2 alkyl); and

R_{12} is hydrogen or C_1-C_4 alkyl;

(a) A is not straight chain C_1-C_{12} alkyl;
(b) when R_3 is hydrogen, A is benzyl or phenethyl, and R_4 is fluoro, chloro, bromo or iodo, then R_5 is not 5'-deoxy-ribofuranosyl or 5'-amino-5'-deoxyribofuranosyl; and
(c) when R^5 is phenyl, said phenyl is substituted by two or three substituents.

II. The invention also relates to use of a CRF antagonist of the following formula, described in WO 94/13676:



and the pharmaceutically acceptable acid addition salts thereof, wherein B is NR_1R_2, $CR_1R_2R_{11}$, C(=CR_2R_{12}) R_1, $NHR_1R_2R_{11}$, $OCR_1R_2R_{11}$, $SCR_1R_2R_{11}$, $NHNR_1R_2$, $CR_2R_{11}NHR_1$, $CR_2R_{11}OR_1$, $CR_2R_{11}SR_1$, or C(O)R_2;

R_1 is hydrogen, or C_1-C_6 alkyl which may be substituted by one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, C_1-C_8 alkoxy, O-C(=O)-(C_1-C_6 alkyl), O-C(=O)NH(C_1-C_4 alkyl), O-C(=O)-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), amino, NH(C_1-C_4 alkyl), N(C_1-C_2 alkyl)(C_1-C_4 alkyl), S(C_1-C_6 alkyl), N(C_1-C_4alkyl)C(=O)(C_1-C_4 alkyl), NH(C_1-C_4 alkyl), COOH, C(=O)O(C_1-C_4 alkyl), C(=O)NH(C_1-C_4 alkyl), C(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, CN, NO_2, $SO(C_1$-C_4 alkyl), $SO_2(C_1$-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), and said C_1-C_6 alkyl may contain one or two double or triple bonds;

R_2 is C_1-C_{12} alkyl, aryl or (C_1-C_{10} alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benziso-thiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopy-ridyl, oxazolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or (C_3-C_6 alkylene) cycloalkyl, wherein said cycloalkyl may contain one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, benzyl or C_1-C_4 alkanoyl, wherein R_2 may be substituted independently by from one to three of chloro, fluoro, or C_1-C_4 alkyl, or one of hydroxy, bromo, iodo, C_1-C_6 alkoxy, O-C(=O)-(C_1-C_6 alkyl), O-C-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), S(C_1-C_6 alkyl), NH_2, NH(C_1-C_2 alkyl), N(C_1-C_2 alkyl) (C_1-C_4 alkyl), N(C_1-C_4)- C(=O)(C_1-C_4 alkyl), NHC(=O)(C_1-C_4), COOH, C(=O)O(C_1-C_4 alkyl), C(=O)NH(C_1-C_4 alkyl), C(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, CN, NO_2, $SO(C_1$-C_4 alkyl), $SO_2(C_1$-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), and wherein said C_1-C_{12} alkyl or C_1-C_{10} alkylene may contain one to three double or triple bonds; or

NR_1R_2 or $CR_1R_2R_{11}$ may form a saturated 3- to 8 membered carbocyclic ring of which the 5- to 8-membered ring contain one or two double bonds or one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, benzyl or C_1-C_4 alkanoyl;

R_3 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, O(C_1-C_6 alkyl), NH(C_1-C_6 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, S(C_1-C_4 alkyl), SO(C_1-C_4 alkyl), or $SO_2(C_1$-C_4 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may contain from one or two double or triple bonds and may be substituted by from 1 to 3 substituents R_8 independently selected from the group consisting of hydroxy, amino, C_1-C_3 alkoxy, dimethyl-amino, diethylamino, methylamino, ethylamino, $NHCH_3$, fluoro, chloro or C_1-C_3 thioalkyl;

R_4 and R_6 are each independently hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, amino, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_2 alkyl), $SO_n(C_1$-C_6 alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, carboxy, or amido, wherein said C_1-C_6 alkyls may be substituted by one to three of hydroxy, amino, carboxy, amido, NHC(=O)(C_1-C_4 alkyl), NH(C_1-C_4 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl), C(=O)O(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

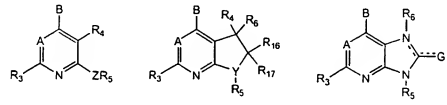
R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, tri-

azolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, piperidinyl, piperazinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, optionally containing one to three of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl or phenylmethyl, wherein each one of the above groups may be substituted independently by from one to four of fluoro, chloro, C_1-C_6 alkyl, C_1-C_6 alkoxy or trifluoromethyl, or one of bromo, iodo, cyano, nitro, amino, NH(C_1-C_4 alkyl), N(C_1-C_4)(C_1-C_2 alkyl), COO(C_1-C_4 alkyl), CO(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_2 alkyl)(C_1-C_2 alkyl), SO_2NH_2, $NHSO_2$(C_1-C_4 alkyl), S(C_1-C_6 alkyl), SO_2(C_1-C_6 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may be substituted by one or two of fluoro, chloro, hydroxy, amino, methylamino, dimethylamino or acetyl; with the proviso that R_8 is not unsubstituted phenyl;

R_{11} is hydrogen, hydroxy, fluoro, chloro, COO(C_1-C_2 alkyl), cyano, or CO(C_1-C_2 alkyl); and

R_{12} is hydrogen or C_1-C_4 alkyl; with the proviso that (1) when R_5 is 4-bromophenyl, R_3 is hydrogen, and R_4 and R_6 are methyl, then B is not methylamino or ethyl, and (2) when R_5 is 4-bromophenyl, and R_3, R_4 and R_6 are methyl, then B is not 2-hydroxyethylamino.

III. It is also possible to employ a CRF antagonist that has a structure selected from the group shown below, and pharmaceutically acceptable salts and esters thereof, as described in WO 95/33750:



or a pharmaceutically acceptable salt thereof, wherein

the dashed lines represent optional double bonds;

A is CR_3 or N;

B is NR_1R_2, $CR_1R_2R_{11}$, C(=CR_2R_{12})R_1, $NHCHR_1R_2$, $OCHR_1R_2$, $SCHR_1R_2$, CHR_2OR_{12}, CHR_2SR_{12}, C(S)R_2 or C(O)R_2;

G is oxygen, sulfur, NH, NH_3, hydrogen, methoxy, ethoxy, trifluoromethoxy, methyl, ethyl, thiomethoxy, NH_2, $NHCH_3$, $N(CH_3)_2$ or trifluoromethyl;

Y is CH or N;

Z is NH, O, S, N (C_1-C_2 alkyl), or $CR_{13}R_{14}$, wherein R_{13} and R_{14} are each independently hydrogen, trifluoromethyl, or C_1-C_4 alkyl, or one of R_{13} and R_{14} may be cyano, chloro, bromo, iodo, fluoro, hydroxy, O(C_1-C_2 alkyl), amino, NH(C_1-C_2 alkyl), or $CR_{13}R_{14}$ may be C=O or cyclopropyl;

R_1 is C_1-C_6 alkyl which may be substituted by one or two substituents R_8 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, O-CO-(C_1-C_4 alkyl), O-CO-NH(C_1-C_4 alkyl), O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), NH(C_1-C_4 alkyl), N(C_1-C_2 alkyl)(C_1-C_4 alkyl), S(C_1-C_4 alkyl), N(C_1-C_4alkyl)CO(C_1-C_4 alkyl), NHCO(C_1-C_4 alkyl), COO(C_1-C_4 alkyl), CONH(C_1-C_4 alkyl), CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), S(C_1-C_4 alkyl), CN, NO_2, SO(C_1-C_4 alkyl), SO_2(C_1-C_4 alkyl), and said C_1-C_6 alkyl or C_1-C_4 alkyl may contain one double or triple bond;

R_2 is C_1-C_{12} alkyl, aryl or (C_1-C_4 alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or (C_1-C_6 alkylene)cycloalkyl, wherein said cycloalkyl may contain one or two of O, S or N-R_9 wherein R_9 is hydrogen, or C_1-C_4 alkyl, wherein the above defined R_2 may be substituted independently by from one to three of chloro, fluoro, or C_1-C_4 alkyl, or one of bromo, iodo, C_1-C_6 alkoxy, O-CO-(C_1-C_6 alkyl), O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), S(C_1-C_6 alkyl), CN, NO_2, SO(C_1-C_4 alkyl), or SO_2(C_1-C_4 alkyl), and wherein said C_1-C_{12} alkyl or C_1-C_4 alkylene may contain one double or triple bond; or

NR_1R_2 or $CR_1R_2R_{11}$ may form a saturated 5- to 8-membered carbocyclic ring which may contain one or two double bonds or one or two of O or S;

R_3 is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF_3, methylthio, methylsulfonyl, CH_2OH or CH_2OCH_3;

R_4 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, amino, nitro, NH(C_1-C_4 alkyl), N(C_1-C_4

alkyl)(C_1-C_2 alkyl), SO_n(C_1-C_4 alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, CO(C_1-C_4 alkyl), CHO, or COO (C_1-C_4 alkyl), wherein said C_1-C_4 alkyl may contain one or two double or triple bonds and may be substituted by one or two of hydroxy, amino, carboxy, $NHCOCH_3$, NH(C_1-C_2 alkyl), N(C_1-C_2 alkyl)$_2$, COO(C_1-C_4 alkyl), CO(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, chloro, cyano or nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, furanyl, benzofuranyl, benzothiazolyl, or indolyl, wherein each one of the above groups R_5 is substituted independently by from one to three of fluoro, chloro, C_1-C_6 alkyl, or C_1-C_6 alkoxy, or one of hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, NH(C_1-C_4 alkyl), N(C_1-C_6)(C_1-C_2 alkyl), COOH, COO(C_1-C_4 alkyl), CO(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SO_2NH_2, $NHSO_2$(C_1-C_4 alkyl), S(C_1-C_6 alkyl), or SO_2 (C_1-C_6 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may be substituted by one or two of fluoro, hydroxy, amino, methylamino, dimethylamino or acetyl;

R_6 is hydrogen, or C_1-C_6 alkyl, wherein said C_1-C_6 alkyl may be substituted by one hydroxy, methoxy, ethoxy or fluoro;

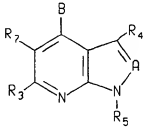
R_7 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, O(C_1-C_4 alkyl), C(O)(C_1-C_4 alkyl), or C(O)O(C_1-C_4 alkyl), wherein the C_1-C_4 alkyl groups may be substituted with one hydroxy, chloro or bromo, or one to three fluoro;

R_{11} is hydrogen, hydroxy, fluoro, or methoxy;

R_{12} is hydrogen or C_1-C_4 alkyl; and

R_{16} and R_{17} are each independently hydrogen, hydroxy, methyl, ethyl, methoxy, or ethoxy, except that they are not both methoxy or ethoxy, and CR_4R_6 and $CR_{16}R_{17}$ each independently may be C=O.

IV. It also possible to employ a CRF antagonist of the following formula, disclosed in WO 95/34563:



and the pharmaceutically acceptable acid addition salts thereof, wherein

A is N or -CR_6;

B is -NR_1R_2, -$CR_1R_2R_{11}$, -C(=CR_2R_{12})R_1, -NHCHR_1R_2, -OCHR_1R_2, -SCHR_1R_2, -CHR_2OR_{12}, -CHR_2SR_{12}, -C(S)R_1 or -C(O)R_1;

R_1 is C_1-C_6 alkyl which may optionally be substituted with one or two substituents independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH (C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON (C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), and wherein any of the foregoing C_1-C_4 alkyl and C_1-C_6 alkyl groups may optionally contain one carbon-carbon double or triple bond;

R_2 is C_1-C_{12} alkyl, aryl, -(C_1-C_4 alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, oxazolyl, or benzoxazolyl; or 3- to 8- membered cycloalkyl or -(C_1-C_6 alkylene)cycloalkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said -(C_1-C_6 alkylene)cycloalkyl having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom or by N-Z wherein Z is hydrogen; or C_1-C_4 alkyl, and wherein each of said groups R_2 may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, and C_1-C_4 alkyl, or by one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -O-CO-(C_1-C_6 alkyl), -S(C_1-C_6 alkyl), -COO(C_1-C_4 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl), and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_{12} alkyl and the C_1-C_4 alkylene moiety of said -(C_1-C_4 alkylene)aryl may optionally contain one carbon-carbon double or triple bond;

or -NR_1R_2 may form a saturated 5- to 8-membered heterocyclic ring, or -CHR_1R_2 may form a saturated 5- to

8-membered carbocyclic ring, wherein each of these rings may optionally contain one or two carbon-carbon double bonds and wherein one or two of the carbon atoms of each of these rings may optionally be replaced with a sulfur or oxygen atom;

R_3 is C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, $-CH_2OH$, $-CH_2OCH_3$, $-O(C_1$-C_3 alkyl), $-S(C_1$-C_3 alkyl), or $-SO_2(C_1$-C_3 alkyl), wherein said C_1-C_3 alkyl may optionally contain one carbon-carbon double or triple bond;

R_4 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, amino, $-NHCH_3$, $-N(CH_3)_2$, $-CH_2OH$, $-CH_2OCH_3$, or $-SO_n(C_1$-C_4 alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, $-CO(C_1$-C_4 alkyl), -CHO, or $-COO(C_1$-C_4 alkyl) wherein the C_1-C_4 alkyl moieties in the foregoing R_4 groups may optionally contain one carbon-carbon double or triple bond;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, pyrimidyl, benzofuranyl, pyrazinyl or benzothiazolyl, wherein each one of said groups R_5 may optionally be substituted with from one to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl and C_1-C_6 alkoxy, or by one substituent selected from iodo, hydroxy, bromo, formyl, cyano, nitro, amino, trifluoromethyl, $-NH(C_1$-C_4 alkyl), $-N(C_1$-$C_6)(C_1$-C_2 alkyl), $-COO(C_1$-C_4 alkyl), $-CO(C_1$-C_4 alkyl), -COOH, $-SO_2NH(C_1$-C_4 alkyl), $-SO_2N(C_1$-C_4 alkyl)$(C_1$-C_2 alkyl), $-SO_2NH_2$, $-NHSO_2(C_1$-C_4 alkyl), $-S(C_1$-C_6 alkyl) and $-SO_2(C_1$-C_6 alkyl), wherein each of said C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the foregoing R^3 groups may optionally be substituted with one to three fluorine atoms;

R_6 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, $-CH_2OH$, $-CH_2OCH_3$, or C_1-C_4 alkoxy;

R_9 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, $-O(C_1$-C_4 alkyl), cyano, $-CH_2OH$, $-CH_2O(C_1$-C_2 alkyl), $-CO(C_1$-C_2 alkyl), or $-COO(C_1$-C_2 alkyl);

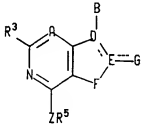
R_{11} is hydrogen, hydroxy, fluoro, or methoxy; and

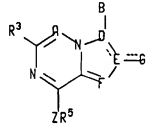
R_{12} is hydrogen or C_1-C_4 alkyl;

with the proviso that when A is N, then: (a) B is not unsubstituted alkyl; (b) R_5 is not unsubstituted phenyl or monosubstituted phenyl; and (c) R_3 is not unsubstituted alkyl;

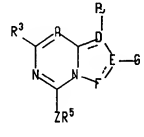
or a pharmaceutically acceptable salt of such compound.

V. In another embodiment, the CRF antagonist is of the following formula, disclosed in EP 778277:





or



or a pharmaceutically acceptable salt thereof, wherein

the dashed lines represent optional double bonds;

A is nitrogen or CR^7;

B is $-NR^1R^2$, $-CR^1R^2R^{10}$, $-C(=CR^2R^{11})R^1$, $-NHCR^1R^2R^{10}$, $-OCR^1R^2R^{10}$, $-SCR^1R^2R^{10}$, $-CR^2R^{10}NHR^1$, $-CR^2R^{10}OR^1$, $-CR^2R^{10}SR^1$ or $-COR^2$;

D is nitrogen and is single bonded to all atoms to which it is attached, or D is carbon and is either double bonded to E in formulas I and II or double bonded to the adjacent carbon atom common to both fused rings in formula III, or D is CH and is single bonded to E in formulas I and II;

E is nitrogen, CH or carbon;

F is oxygen, sulfur, CHR^4 or NR^4 when it is single bonded to E and F is nitrogen or CR^4 when it is double bonded to E;

G, when single bonded to E, is hydrogen, C_1-C_4 alkyl, -S(C_1-C_4 alkyl), -O(C_1-C_4 alkyl), NH_2, -NH(C_1-C_4 alkyl) or -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), wherein each of the C_1-C_4 alkyl groups of G may optionally be substituted with one hydroxy, -O(C_1-C_2 alkyl) or fluoro group; G, when double bonded to E, is oxygen, sulfur or NH; and G, when E is nitrogen and double bonded to D or F, is absent;

R^1 is hydrogen, C_1-C_6 alkyl optionally substituted with one or two substituents R^8 independently selected from hydroxy, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, CF_3, -C(=O)O-(C_1-C_4)alkyl, -OC(=O)(C_1-C_4 alkyl), -OC(=O)N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_2 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -CN, -NO_2, -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl) and -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), wherein each of the C_1-C_4 alkyl groups in the foregoing R^1 groups may optionally contain one or two double or triple bonds;

R^2 is C_1-C_{12} alkyl which may optionally contain from one to three double or triple bonds, aryl or (C_1-C_4 alkylene) aryl, wherein said aryl and the aryl moiety of said (C_1-C_4 alkylene)aryl is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; C_3-C_8 cycloalkyl or (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl), wherein one or two of the carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl) may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^2 wherein Z^2 is selected from hydrogen, C_1-C_4 alkyl, benzyl and C_1-C_4 alkanoyl, and wherein each of the foregoing R^2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, hydroxy and C_1-C_4 alkyl, or with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -OC(=O)(C_1-C_6 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), amino, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)-CO-(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SH, -CN,-NO_2, -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl) and -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl);

-NR^1R^2 or $CR^1R^2R^{10}$ may form a saturated 3 to 8 membered carbocyclic ring which may optionally contain from one to three double bonds and wherein one or two of the ring carbon atoms of such 5 to 8 membered rings may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^3 wherein Z^3 is hydrogen, C_1-C_4 alkyl, benzyl or C_1-C_4 alkanoyl;

R^3 is hydrogen, C_1-C_4 alkyl, -O(C_1-C_4 alkyl), chloro, fluoro, bromo, iodo, -CN, -S(C_1-C_4 alkyl) or -SO_2(C_1-C_4 alkyl) wherein each of the (C_1-C_4 alkyl) moieties in the foregoing R^3 groups may optionally be substituted with one substituent R^9 selected from hydroxy, fluoro and (C_1-C_2 alkoxy);

each R^4 is, independently, hydrogen, (C_1-C_6 alkyl), fluoro, chloro, bromo, iodo, hydroxy, cyano, amino, nitro, -O(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl),-S(C_1-C_4 alkyl), -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4)alkyl, -CO(C_1-C_4 alkyl), -C(=O)H or -C(=O)O(C_1-C_4alkyl), wherein each of the (C_1-C_6 alkyl) and (C_1-C_4 alkyl) moieties in the foregoing R^4 groups may optionally contain one or two double or triple bonds and may optionally be substituted with one or two substituents independently selected from hydroxy, amino, C_1-C_3 alkoxy, dimethylamino, methylamino, ethylamino, -NHC(=O)CH_3, fluoro, chloro, C_1-C_3 thioalkyl, -CN, -COOH,-C(=O)O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl) and -NO_2;

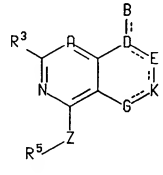
R^5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, benzoxazolyl or C_3-C_8 cycloalkyl wherein one or two of the carbon atoms of said cycloalkyl rings that contain at least 5 ring members may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^4 wherein Z^4 is hydrogen, C_1-C_4 alkyl or benzyl; and wherein each of the foregoing R^5 groups is substituted with from one to four substituents R^{12} wherein one to three of said substituents may be selected, independently, from chloro, C_1-C_6 alkyl and-O(C_1-C_6 alkyl) and one of said substituents may be selected from bromo, iodo, formyl, -CN, -CF_3, -NO_2, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_6 alkyl),-C(=O)O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl), -COOH, -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -SO_2NH_2, -$NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and -SO_2(C_1-C_6 alkyl), and wherein each of the C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the foregoing R^5 groups may optionally be substituted with one or two substituents independently selected from fluoro, hydroxy, amino, methylamino, dimethylamino and acetyl;

R^7 is hydrogen, C_1-C_4 alkyl, halo, cyano, hydroxy, -O(C_1-C_4 alkyl) -C(=O)(C_1-C_4 alkyl), -C(=O)O(C_1-C_4alkyl), -OCF_3, -CF_3, -CH_2OH, -CH_2O(C_1-C_4 alkyl);

R^{10} is hydrogen, hydroxy, methoxy or fluoro;

R^{11} is hydrogen or C_1-C_4 alkyl; and
Z is NH, oxygen, sulfur, -N(C_1-C_4 alkyl), -NC(=O)(C_1-C_2 alkyl), NC(=O)O(C_1-C_2alkyl) or $CR^{13}R^{14}$ wherein R^{13} and R^{14} are independently selected from hydrogen, trifluoromethyl and methyl with the exception that one of R^{13} and R^{14}can be cyano;
with the proviso that: (a) in the five membered rings of structures I, II and III, there can not be two double bonds adjacent to each other; and (b) when R^4 is attached to nitrogen, it is not halo, cyano or nitro;
or a pharmaceutically acceptable salt of such compound.

VI. The CRF antagonist can also be of the following formula, disclosed in WO 98/05661:



wherein the dashed lines represent optional double bonds;

A is nitrogen or CR^7;
B is -NR^1R^2, -$CR^1R^2R^{10}$, -C(=CR^2R^{11})R^1, -$NHCR^1R^2R^{10}$, -$OCR^1R^2R^{10}$, -$SCR^1R^2R^{10}$, -$CR^2R^{10}NHR^1$, -$CR^2R^{10}OR^1$, -$CR^2R^{10}SR^1$ or -COR^2, and is single bonded to D; or B is -CR^1R^2, and is double bonded to D and D is carbon;
D is nitrogen or CR^4 and is single bonded to all atoms to which it is attached, or D is carbon and is double bonded to E or double bonded to B;
E is oxygen, nitrogen, sulfur, C=O, C=S, CR^6R^{12}, NR^6 or CR^6; or E is a two atom spacer, wherein one of the atoms is oxygen, nitrogen, sulfur, C=O, C=S, CR^6R^{12}, NR^6 or CR^6, and the other is CR^6R^{12} or CR^9;
K and G are each, independently, C=O, C=S, sulfur, oxygen, CHR^8 or NR^8 when single bonded to both adjacent ring atoms, or nitrogen or CR^8 when it is double bonded to an adjacent ring atom;
the 6- or 7-membered ring that contains D, E, K and G may contain from one to three double bonds, from zero to two heteroatoms selected from oxygen, nitrogen and sulfur, and from zero to two C=O or C=S groups, wherein the carbon atoms of such groups are part of the ring and the oxygen and sulfur atoms are substituents on the ring;
R^1 is C_1-C_6 alkyl optionally substituted with from one or two substituents independently selected from hydroxy, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, CF_3, -C(=O)(C_1-C_4alkyl), -C(=O)-O-(C_1-C_4)alkyl, -OC(=O)(C_1-C_4 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -CN, -NO_2, -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl) and -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), wherein each of the C_1-C_4 alkyl groups in the foregoing R^1 groups may optionally contain one or two double or triple bonds;
R^2 is C_1-C_{12} alkyl which may optionally contain from one to three double or triple bonds, aryl or (C_1-C_4 alkylene) aryl, wherein said aryl and the aryl moiety of said (C_1-C_4 alkylene)aryl is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; C_3-C_8 cycloalkyl or (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl), wherein one or two of the carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl may optionally and independently be replaced by an oxygen or sulfur and wherein each of the foregoing R^2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, hydroxy and C_1-C_4 alkyl, or with one substituent selected from C_1-C_6 alkoxy, -OC(=O)(C_1-C_6 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), amino, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)-CO-(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SH, -CN, -NO_2, -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl) and -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl);

$-NR^1R^2$ or $CR^1R^2R^{10}$ may form a ring selected from saturated 3 to 8 membered rings, the 5 to 8 membered rings of which may optionally contain one or two double bonds, and wherein one or two of the ring carbon atoms of such 5 to 8 membered rings may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^3 wherein Z^3 is hydrogen or C_1-C_4 alkyl;

R^3 is hydrogen, C_1-C_4 alkyl, -O(C_1-C_4 alkyl), chloro, fluoro, bromo, iodo, -S(C_1-C_4 alkyl) or -SO_2(C_1-C_4 alkyl);

R^4 is hydrogen, C_1-C_2 alkyl, hydroxy or fluoro;

each R^6, R^8 and R^9 that is attached to a carbon atom is selected, independently, from hydrogen, C_1-C_2 alkyl, fluoro, chloro, bromo, iodo, hydroxy, hydroxymethyl, formyl, trifluoromethyl, cyano, amino, nitro, -O(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)(C_1-C_2 alkyl), -S(C_1-C_2 alkyl), -CO(C_1-C_2 alkyl), -C(=O)H or -C(=O)O(C_1-C_2 alkyl), wherein each of the C_1-C_2 alkyl moieties in the foregoing R^6, R^8, and R^9 groups may optionally contain one double or triple bond; and each R^6, R^8, and R^9 that is attached to a nitrogen atom is selected, independently, from hydrogen and C_1-C_4 alkyl;

R^5 is substituted phenyl, naphthyl, pyridyl or pyrimidyl, wherein each of the foregoing R^5 groups is substituted with from two to four substituents R^{15}, wherein from one to three of said substituents may be selected, independently, from chloro, C_1-C_6 alkyl, -O(C_1-C_6 alkyl) and -(C_1-C_6alkylene)O(C_1-C_6alkyl), and wherein one of said substituents may be selected, independently, from bromo, iodo, formyl, cyano, trifluoromethyl, nitro, amino, -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_6 alkyl), -C(=O)O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl), -COOH, -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -SO_2NH_2, -$NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and -SO_2(C_1-C_6 alkyl), and wherein each of the C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the foregoing R^5 groups may optionally be substituted with one or two substituents independently selected from fluoro, hydroxy, amino, methylamino, dimethylamino and acetyl;

R^7 is hydrogen, methyl, halo (e.g., chloro, fluoro, iodo or bromo), hydroxy, methoxy, -C(=O)(C_1-C_2 alkyl), -C(=O)O(C_1-C_2 alkyl), trifluoromethoxy, hydroxymethyl, trifluoromethyl or formyl;

R^{10} is hydrogen, hydroxy, methoxy or fluoro;

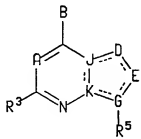
R^{11} is hydrogen or C_1-C_4 alkyl;

R^{12} is hydrogen or methyl; and

Z is NH, oxygen, sulfur, -N(C_1-C_4 alkyl), or $CR^{13}R^{14}$ wherein R^{13} and R^{14} are independently selected from hydrogen, and methyl with the exception that one of R^{13} and R^{14} may optionally be cyano;

with the proviso that: (a) in the six or seven membered rings of structures in formula I, there can not be two double bonds adjacent to each other; and (b) when D is carbon and is double bonded to B, then B is CR^1R^2; or a pharmaceutically acceptable salt of such compound.

VII. The CRF antagonist can also be of the following formula, disclosed in WO 98/08847:



or a pharmaceutically acceptable salt thereof, wherein

the dashed lines represent optional double bonds;

A is nitrogen or CR^7;

B is $-NR^1R^2$, $-CR^1R^2R^{10}$ $-C(=CR^2R^{11})R^1$, $-NHCR^1R^2R^{10}$, $-OCR^1R^2R^{10}$, $-SCR^1R^2R^{10}$, $-CR^2R^{10}NHR^1$, $-CR^2R^{10}OR^1$, $-CR^2R^{10}SR^1$ or $-COR^2$;

J and K are each independently nitrogen or carbon and both J and K are not nitrogens;

D and E are each selected, independently, from nitrogen, CR^4, C=O, C=S, sulfur, oxygen, CR^4R^6 and NR^8;

G is nitrogen or carbon;

the ring containing D, E, G, K, and J in formula I may be a saturated or unsaturated 5-membered ring and may optionally contain one or two double bonds and may optionally contain from one to three heteroatoms in the ring and may optionally have one or two C=O or C=S groups;

R^1 is C_1-C_6 alkyl optionally substituted with one or two substituents independently selected from hydroxy, fluoro, chloro, bromo, iodo, -O-(C_1-C_4 alkyl), CF_3, -C(=O)O-(C_1-C_4alkyl), -OC(=O)(C_1-C_4 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -CN, $-NO_2$, -SO(C_1-C_4 alkyl), $-SO_2$(C_1-C_4 alkyl), $-SO_2NH$(C_1-C_4 alkyl) and $-SO_2N$(C_1-C_4 alkyl)(C_1-C_2 alkyl), wherein each of the C_1-C_4 alkyl groups in the foregoing R^1 groups may optionally contain one or two double or triple bonds;

R^2 is C_1-C_{12} alkyl which may optionally contain from one to three double or triple bonds, aryl or (C_1-C_4 alkylene) aryl, wherein said aryl and the aryl moiety of said (C_1-C_4 alkylene)aryl is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; C_3-C_8 cycloalkyl or (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl), wherein one or two of the carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl) may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^2 wherein Z^2 is selected from hydrogen, C_1-C_4 alkyl, benzyl and C_1-C_4 alkanoyl, and wherein each of the foregoing R^2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, hydroxy and C_1-C_4 alkyl, or with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -OC(=O)(C_1-C_6 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), amino, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)(C_1-C_2 alkyl), -N(C_1-C_4 alkyl)-CO-(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SH, -CN, $-NO_2$, -SO(C_1-C_4 alkyl), $-SO_2$(C_1-C_4 alkyl), $-SO_2NH$(C_1-C_4 alkyl) and $-SO_2N$(C_1-C_4 alkyl)(C_1-C_2 alkyl);

$-NR^1R^2$ or $CR^1R^2R^{10}$ may form a saturated 3 to 8 membered carbocyclic ring which may optionally contain from one to three double bonds and wherein one or two of the ring carbon atoms of such 5 to 8 membered rings may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^3 wherein Z^3 is hydrogen, C_1-C_4 alkyl, benzyl or C_1-C_4 alkanoyl;

R^3 is hydrogen, C_1-C_4 alkyl, -O(C_1-C_4 alkyl), chloro, fluoro, bromo, iodo, (C_1-C_2 alkylene)-O-(C_1-C_2 alkyl), (C_1-C_2 alkylene)-OH, or -S(C_1-C_4 alkyl);

each R^4 is, independently, hydrogen, (C_1-C_6 alkyl), fluoro, chloro, bromo, iodo, hydroxy, cyano, amino, (C_1-C_2 alkylene)-OH, CF_3, CH_2SCH_3, nitro, -O(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -C(=O)H or -C(=O)O(C_1-C_4alkyl);

R^6 is hydrogen, methyl or ethyl;

R^8 is hydrogen or C_1-C_4 alkyl;

R^5 is phenyl, pyridyl, pyrazinyl, pyrimidyl, pyridazinyl and wherein each of the foregoing R^5 groups is substituted with from one to four substituents R^{13} wherein one to three of said substituents may be selected, independently, from fluoro, chloro, C_1-C_6 alkyl and -O(C_1-C_6 alkyl) and one of said substituents may be selected from bromo, iodo, formyl, OH, (C_1-C_4 alkylene)-OH, (C_1-C_4alkylene)-O-(C_1-C_2 alkyl), -CN, $-CF_3$, $-NO_2$, $-NH_2$, -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_6 alkyl), -OCO(C_1-C_4 alkyl), (C_1-C_4 alkylene)-O-(C_1-C_4 alkyl), -S(C_1-C_6 alkyl), (C_1-C_4 alkylene)-S-(C_1-C_4 alkyl), -C(=O)O(C_1-C_4 alkyl), -C(=O)O(C_1-C_4 alkyl), -COOH, $-SO_2NH$(C_1-C_4 alkyl), $-SO_2N$(C_1-C_2 alkyl)(C_1-C_4 alkyl), $-SO_2NH_2$, $-NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and $-SO_2$(C_1-C_6 alkyl), and wherein each of the C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the foregoing R^5 groups may optionally have one or two double bonds;

R^7 is hydrogen, C_1-C_4 alkyl, halo (e.g., chloro, fluoro, iodo or bromo), hydroxy, -O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl), -C(=O)O(C_1-C_4 alkyl), $-OCF_3$, $-CF_3$, $-CH_2OH$ or $-CH_2O$(C_1-C_2 alkyl);

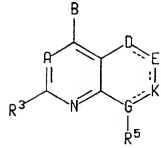
R^{10} is hydrogen, hydroxy, methoxy or fluoro;

R^{11} is hydrogen or C_1-C_4 alkyl; and

with the proviso that: a) when both J and K are carbons and D is CR^4 and E is nitrogen, then G can not be nitrogen; (b) when both J and K are carbons and D and G are nitrogens, then E can not be CR^4 or C=O or C=S; (c) when both J and K are carbons and D and E are carbons, then G can not be nitrogen; (d) when G is carbon, it must be double banded to E; and (e) in the ring containing J, K, D, E and G, there can not be two double bonds adjacent to each other;

and the pharmaceutically acceptable salts of such compounds.

VIII. Other useful CRF antagonists are of the following formula, disclosed in WO 98/08846:



wherein the dashed lines represent optional double bonds;

A is nitrogen or CR^7;

B is $-NR^1R^2$, $-CR^1R^2R^{10}$, $-C(=CR^2R^{11})R^1$, $-NHCR^1R^2R^{10}$, $-OCR^1R^2R^{10}$, $-SCR^1R^2R^{10}$, $-CR^2R^{10}NHR^1$, $-CR^2R^{10}OR^1$, $-CR^2R^{10}SR^1$ or $-COR^2$;

G is nitrogen or CR^4 and is single bonded to all atoms to which it is attached, or G is carbon and is double bonded to K;

K is nitrogen or CR^6 when double bonded to G or E, or K is oxygen, sulfur, C=O, C=S, CR^6R^{12} or NR^8 when single bonded to both adjacent ring atoms, or K is a two atom spacer, wherein one of the two ring atoms of the spacer is oxygen, nitrogen, sulfur, C=O, C=S, CR^6R^{12}, NR^6 or CR^6, and the other is CR^6R^{12} or CR^6;

D and E are each, independently, C=O, C=S, sulfur, oxygen, CR^4R^6 or NR^8 when single bonded to both adjacent ring atoms, or nitrogen or CR^4 when it is double bonded to an adjacent ring atom;

the 6- or 7-membered ring that contains D, E, K and G may contain from one to three double bonds, from zero to two heteroatoms selected from oxygen, nitrogen and sulfur, and from zero to two C=O or C=S groups, wherein the carbon atoms of such groups are part of the ring and the oxygen and sulfur atoms are substituents on the ring;

R^1 is C_1-C_6 alkyl optionally substituted with from one or two substituents independently selected from hydroxy, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, CF_3, $-C(=O)(C_1$-C_4alkyl), $-C(=O)$-O-(C_1-C_4)alkyl, $-OC(=O)(C_1$-C_4 alkyl), $-OC(=O)N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), $-NHCO(C_1$-C_4 alkyl), $-COOH$, $-COO(C_1$-C_4 alkyl), $-CONH(C_1$-C_4 alkyl), $-CON(C_1$-C_4 alkyl)(C_1-C_2 alkyl), $-S(C_1$-C_4 alkyl), $-CN$, $-NO_2$, $-SO(C_1$-C_4 alkyl), $-SO_2(C_1$-C_4 alkyl), $-SO_2NH(C_1$-C_4 alkyl) and $-SO_2N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), wherein each of the C_1-C_4 alkyl groups in the foregoing R^1 groups may optionally contain one or two double or triple bonds;

R^2 is C_1-C_{12} alkyl which may optionally contain from one to three double or triple bonds, aryl or (C_1-C_4 alkylene) aryl, wherein said aryl and the aryl moiety of said (C_1-C_4 alkylene)aryl is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; C_3-C_8 cycloalkyl or (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl), wherein one or two of the carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl may optionally and independently be replaced by an oxygen or sulfur atom or by NZ wherein Z is hydrogen, C_1-C_4 alkyl or benzyl, and wherein each of the foregoing R^2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, hydroxy and C_1-C_4 alkyl, or with one substituent selected from C_1-C_6 alkoxy, $-OC(=O)(C_1$-C_6 alkyl), $-OC(=O)N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), $-S(C_1$-C_6 alkyl), amino, $-NH(C_1$-C_2 alkyl), $-N(C_1$-C_2 alkyl)(C_1-C_4 alkyl), $-N(C_1$-C_4 alkyl)-CO-(C_1-C_4 alkyl), $-NHCO(C_1$-C_4 alkyl), $-COOH$, $-COO(C_1$-C_4 alkyl), $-CONH(C_1$-C_4 alkyl), $-CON(C_1$-C_4 alkyl)(C_1-C_2 alkyl), $-SH$, $-CN$, $-NO_2$, $-SO(C_1$-C_4 alkyl), $-SO_2(C_1$-C_4 alkyl), $-SO_2NH(C_1$-C_4 alkyl) and $-SO_2N(C_1$-C_4 alkyl)(C_1-C_2 alkyl);

$-NR^1R^2$ or $CR^1R^2R^{10}$ may form a ring selected from saturated 3 to 8 membered rings, the 5 to 8 membered rings of which may optionally contain one or two double bonds, and wherein one or two of the ring carbon atoms of such 5 to 8 membered rings may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^2 wherein Z^2 is hydrogen, benzyl or C_1-C_4 alkyl;

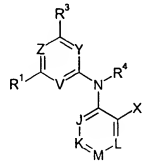
R^3 is hydrogen, C_1-C_4 alkyl, $-O(C_1$-C_4 alkyl), chloro, fluoro, bromo, iodo, $-S(C_1$-C_4 alkyl) or $-SO_2(C_1$-C_4 alkyl);

each R^8, R^9 and R^{12} is selected, independently, from hydrogen and C_1-C_2 alkyl;

each R^4 and R^6 that is attached to a carbon atom is selected, independently, from hydrogen and C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, hydroxy, hydroxy (C_1-C_2 alkyl), trifluoromethyl, cyano, amino, nitro, $-O(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), $-CH_2SCH_3$, $-S(C_1$-C_4 alkyl), $-CO(C_1$-C_4 alkyl), $-C(=O)H$ or $-C(=O)O(C_1$-C_4 alkyl), wherein each of the C_1-C_2 alkyl moieties in the foregoing R^4 and R^6 groups may optionally contain one double

or triple bond; and R^6, when attached to a nitrogen atom, is selected from hydrogen and C_1-C_4 alkyl;
R^5 is substituted phenyl, naphthyl, pyridyl or pyrimidyl, wherein each of the foregoing R^5 groups is substituted with from two to four substituents R^{13}, wherein up to three of said substituents may be selected, independently, from chloro, C_1-C_6 alkyl, -O(C_1-C_6 alkyl) and -(C_1-C_6 alkylene)O(C_1-C_6alkyl), and wherein one of said substituents may be selected, independently, from bromo, iodo, formyl, cyano, trifluoromethyl, nitro, amino, -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_6 alkyl), -C(=O)O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl), -COOH, -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -SO_2NH_2, -NHSO_2(C_1-C_4 alkyl), -(C_6-C_{14}arylene)-S-(C_1-C_2alkyl), -(C_6-C_{14}arylene)-SO-(C_1-C_2alkyl), -(C_6-C_{14}arylene)-SO_2-(C_1-C_2alkyl) and -(C_1-C_4alkylene)-OH, and wherein each of the C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the foregoing R^5 groups may optionally be substituted with one or two substituents independently selected from fluoro, hydroxy, amino, methylamino, dimethylamino and acetyl;
R^7 is hydrogen, methyl, halo (e.g., chloro, fluoro, iodo or bromo), hydroxy, methoxy, -C(=O)(C_1-C_2 alkyl), -C(=O)O(C_1-C_2 alkyl), hydroxymethyl, trifluoromethyl or formyl;
R^{10} is hydrogen, hydroxy, methoxy or fluoro; and
R^{11} is hydrogen or C_1-C_4 alkyl;
with the proviso that in the ring containing D, E, K and G of formula I, there can not be two double bonds adjacent to each other;
and the pharmaceutically acceptable salt of such compound.

IX. The CRF antagonist may also be of the following formula, disclosed in WO 95/10506:



or a pharmaceutically acceptable salt or prodrug thereof, wherein Y is CR^{3a}, N, or CR^{29};

when Y is CR^{3a} or N:
R^1 is independently selected at each occurrence from the group consisting of C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halogen, C_1-C_2 haloalkyl, NR^6R^7, OR^8, and $S(O)_nR^8$;
R^3 is C_1-C_4 alkyl, aryl, C_3-C_6 cycloalkyl, C_1-C_2 haloalkyl, halogen, nitro, NR^6R^7, OR^8, $-S(O)_nR^8$ C(=O)R^9, C(=O)NR^6R^7, C(=S)NR^6R^7, -(CHR^{16})$_k$$NR^6R^7$, -($CH_2$)$_k$$OR^8$, C(=O)$NR^{10}CH(R^{11})CO_2R^{12}$, C(OH)($R^{25}$)($R^{25a}$), -($CH_2$)$_b$S(O)$_n$-alkyl, -($CHR^{16}$)$R^{25}$, -C(N)($R^{25}$)($R^{16}$) provided that R^{25} is not -NH- containing rings, -C(=O)R^{25}, -CH(CO_2R^{16})$_2$, $NR^{10}C(=O)CH(R^{11})NR^{10}R^{12}$, $NR^{10}CH(R^{11})CO_2R^{12}$; substituted C_1-C_4 alkyl, substituted C_2-C_4 alkenyl, substituted C_2-C_4 alkynyl, substituted C_1-C_4 alkoxy, aryl-(substituted C_1-C_4) alkyl, aryl-(substituted C_1-C_4) alkoxy, substituted C_3-C_6 cycloalkyl, amino-(substituted C_1-C_4)alkyl, substituted C_1-C_4 alkylamino, where substitution by R^{27} can occur on any carbon containing substituent; 2-pyridinyl, imidazolyl, 3-pyridinyl, 4-pyridinyl, 2-methyl-3-pyridinyl, 4-methyl-3-pyridinyl, furanyl, 5-methyl-2-furanyl, 2,5-dimethyl-3-furanyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-pheno-thiazinyl, 4-pyrazinyl, azetidinyl, phenyl, 1H-indazolyl, 2-pyrrolidonyl, 2H,6H-1,5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidonyl, 4aH-carbazolyl, 4H-quinolizinyl, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl, azepinyl, benzofuranyl, benzothiophenyl, carbazolyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, furazanyl, imidazolidinyl, indolinyl, indolizinyl, indolyl, isobenzofuranyl, isochromanyl, isoindolinyl, isoindolyl, isoquinolinyl, benzimidazolyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxazolidinyl, oxazolyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, quinuclidinyl, β-carbolinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, thianthrenyl, thiazolyl, thiophenyl, triazinyl, xanthenyl; or 1-tetrahydroquinolinyl or 2-tetrahydroisoquinolinyl

either of which can be substituted with 0-3 groups chosen from keto and C_1-C_4 alkyl;
J, K, and L are independently selected at each occurrence from the group of N, CH, and CX';
M is CR^5 or N;
V is CR^{1a} or N;
Z is CR^2 or N;
R^1, R^2, and R^{3a} are independently selected at each occurrence from the group consisting of hydrogen, halo, halomethyl, C_1-C_3 alkyl, and cyano;
R^4 is $(CH_2)_mOR^{16}$, C_1-C_4 alkyl, allyl, propargyl, $(CH_2)_mR^{13}$, or $-(CH_2)_mOC(O)R^{16}$;
X is halogen, aryl, heteroaryl, $S(O)_2R^8$, SR^8, halomethyl, $-(CH_2)_pOR^8$, cyano, $-(CHR^{16})_pNR^{14}R^{15}$, -C(=O)R^8, C_1-C_6 alkyl, C_4-C_{10} cycloalkylalkyl, C_1-C_{10}alkenyl, C_2-C_{10}alkynyl, C_2-C_{10}alkoxy, aryl-(C_2-C_{10})-alkyl, C_3-C_6cycloalkyl, aryl-(C_1-C_{10})-alkoxy, nitro, thio-(C_1-C_{10})-alkyl, -C(=NOR^{16})-C_1-C_4-alkyl, -C(=NOR^{16})H, or -C(=O)NR^{14}R^{15}, where substitution by R^{18} can occur on any carbon containing substituents;
X' is independently selected at each occurrence from the group consisting of hydrogen, halogen, aryl, heteroaryl, $S(O)_mR^8$, halomethyl, $-(CHR^{16})_pOR^8$, cyano, $-(CHR^{16})_pNR^{14}R^{15}$, C(=O)R^8, C_1-C_6 alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_1-C_{10}alkoxy, aryl-(C_1-C_{10})-alkyl, C_3-C_6cycloalkyl, aryl-(C_1-C_{10})-alkoxy, nitro, thio-(C_1-C_{10})-alkyl, -C(=NOR^{16})-C_1-C_4-alkyl, -C(= NOR^{16})H, and -C(=O)NR^{14}R^{15}, where substitution by R^{18} can occur on any carbon containing substituents;
R^5 is halo, $-C(=NOR^{16})$-C_1-C_4-alkyl, C_1-C_4alkyl, C_1-C_3 haloalkyl, $-(CHR^{16})_pOR^8$, $-(CHR^{16})_pS(O)_nR^8$, $-(CHR^8)_pNR^{14}R^{15}$, C_3-C_6 cycloalkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, aryl-(C_2-C_{10})-alkyl, aryl-(C_1-C_{10})-alkoxy, cyano, C_3-C_6 cycloalkoxy, nitro, amino- (C_2-C_{10})-alkyl, thio-(C_2-C_{10})-alkyl, $SO_2N(R^8)$, $C(=O)R^8$ -C(=NOR^{16})H, or -C(=O)NR^{14}R^{15}, where substitution by R^{18} can occur on any carbon containing substituents;
R^6 and R^7 are independently selected at each occurrence from the group consisting of hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_1-C_6 alkoxy, (C_4-C_{12})-cycloalkylalkyl, $-(CH_2)_kR^{13}$, $(CHR^{16})_pOR^8$, -(C_1-C_6alkyl)-aryl, heteroaryl, -$S(O)_2$-aryl or -(C_1-C_6alkyl)-heteroaryl or aryl, wherein the aryl or heteroaryl groups are optionally substituted with 1-3 groups selected from the group consisting of hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, NHC(=O)(C_1-C_6 alkyl), NH(C_1-C_6 alkyl)$_2$, N(C_1-C_6 alkyl)$_2$, nitro, carboxy, CO_2(C_1-C_6 alkyl), cyano, and $S(O)_2$-(C_1-C_6-alkyl); or can be taken together to form -$(CH_2)_pA(CH_2)_r$-, optionally substituted with 0-3 R^{17}; or, when considered with the commonly attached nitrogen, can be taken together to form a heterocycle, said heterocycle being substituted on carbon with 1-3 groups consisting of hydrogen, C_1-C_6 alkyl, hydroxy, or C_1-C_6 alkoxy;
A is CH_2, O, NR^{25}, C(=O), $S(O)_m$, N(C(=O)R^{17}), N(R^{19}), C(H)(NR^{14}R^{15}), C(H)(OR^{20}), C(H)(C(=O)R^{21}), or N$(S(O)_nR^{21})$;
R^8 is independently selected at each occurrence from the group consisting of hydrogen; C_1-C_6 alkyl; -(C_4-C_{12}) cycloalkylalkyl; $(CH_2)_tR^{22}$; C_3-C_{10} cycloalkyl; -NR^{6}R^7; aryl; heteroaryl; $-NR^{16}(CH_2)_mR^6R^7$; $-(CH_2)_tR^{25}$; and $(CH_2)_t$heteroaryl or $(CH_2)_t$aryl, either of which can optionally be substituted with 1-3 groups selected from the group consisting of hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, NHC(=O)(C_1-C_6 alkyl), NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, nitro, carboxy, CO_2(C_1-C_6 alkyl), cyano, and $S(O)_2$(C_1-C_6-alkyl);
R^9 is independently selected at each occurrence from R^{10}, hydroxy, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, C_2-C_4 alkenyl, aryl substituted with 0-3 R^{18}, and -(C_1-C_6 alkyl)-aryl substituted with 0-3 R^{18};
R^{10}, R^{16}, R^{23}, and R^{24} are independently selected at each occurrence from hydrogen or C_1-C_4 alkyl;
R^{11} is C_1-C_4 alkyl substituted with 0-3 groups chosen from the following: keto, amino, sulfhydryl, hydroxyl, guanidinyl, p-hydroxyphenyl, imidazolyl, phenyl, indolyl, and indolinyl, or, when taken together with an adjacent R^{10}, are $(CH_2)_t$;
R^{12} is hydrogen or an appropriate amine protecting group for nitrogen or an appropriate carboxylic acid protecting group for carboxyl;
R^{13} is independently selected at each occurrence from the group consisting of CN, OR^{19}, SR^{19}, and C_3-C_8 cycloalkyl;
R^{14} and R^{15} are independently selected at each occurrence from the group consisting of hydrogen, C_4-C_{10} cycloalkyl-alkyl, and R$_{19}$;
R^{17} is independently selected at each occurrence from the group consisting of R^{10}, C_1-C_4 alkoxy, halo, OR^{23}, SR^{23}, NR^{23}R^{24}, and (C_1-C_6) alkyl (C_1-C_4) alkoxy;
R^{18} is independently selected at each occurrence from the group consisting of R^{10}, hydroxy, halogen, C_1-C_2 haloalkyl, C_1-C_4 alkoxy, C(=O)R^{24}, and cyano;
R^{19} is independently selected at each occurrence from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $(CH_2)_mR^{22}$, and aryl substituted with 0-3 R^{18};
R^{20} is independently selected at each occurrence from the group consisting of R^{10}, C(=O)R^{31}, and C_2-C_4 alkenyl;
R^{21} is independently selected at each occurrence from the group consisting of R^{10}, C_1-C_4 alkoxy, NR^{23}R^{24},

and hydroxyl;

R^{22} is independently selected at each occurrence from the group consisting of cyano, OR^{24}, SR^{24}, $NR^{23}R^{24}$, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_nR^{31}$, and $-C(=O)R^{25}$;

R^{25}, which can be optionally substituted with 0-3 R17, is independently selected at each occurrence from the group consisting of phenyl, pyrazolyl, imidazolyl, 2-methyl-3-pyridinyl, 4-methyl-3-pyridinyl, furanyl, 5-methyl-2-furanyl, 2,5-dimethyl-3-furanyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-pheno-thiazinyl, 4-pyrazinyl, azetidinyl, 1H-indazolyl, 2-pyrrolidonyl, 2H,6H-1,5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidonyl, 4aH-carbazolyl, 4H-quinolizinyl, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl, azepinyl, benzofuranyl, benzothiophenyl, carbazolyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, furazanyl, indolinyl, indolizinyl, indolyl, isobenzofuranyl, isochromanyl, isoindolinyl, isoindolyl, isoquinolinyl benzimidazolyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxazolidinyl, oxazolyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazolidinyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, quinuclidinyl, ß-carbolinyl, tetrahydrofuranyl, tetrazolyl, thianthrenyl, thiazolyl, thiophenyl, triazinyl, xanthenyl; and 1 -tetrahydroquinolinyl or 2-tetrahydroisoquinolinyl either of which can be substituted with 0-3 groups chosen from keto and C_1-C_4 alkyl;

R^{25a}, which can be optionally substituted with 0-3 R^{17}, is independently selected at each occurrence from the group consisting of H and R^{25};

R^{27} is independently selected at each occurrence from the group consisting of C_1-C_3 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_2-C_4 alkoxy, aryl, nitro, cyano, halogen, aryloxy and heterocycle optionally linked through 0;

R^{31} is independently selected at each occurrence from the group consisting of C_1-C_4 alkyl, C_3-C_7 cycloalkyl, C_4-C_{10} cycloalkyl-alkyl, and aryl-(C_1-C_4) alkyl;

k, m, and r are independently selected at each occurrence from 1-4;

n is independently, selected at each occurrence from 0-2,

p, q, and z are independently selected at each occurrence from 0-3; t and w are independently selected at each occurrence from 1-6, provided that when J is CX' and K and L are both CH, and M is CR^5, then

(A) when V and Y are N and Z is CH and R^1 and R^3 are methyl,

(1) and R^4 is methyl, then

(a) R^5 can not be methyl when X is OH and X' is H;
(b) R^5 can not be $-NHCH_3$, or $-N(CH_3)_2$ when X and X' are $-OCH_3$; and
(c) R^5 can not be $-N(CH_3)_2$ when X and X' are $-OCH_2CH_3$;

(2) and R^4 is ethyl, then

(a) R^5 can not be methylamine when X and X' are $-OCH_3$;
(b) R^5 can not be OH when X is Br and X' is OH; and
(c) R^5 can not be $-CH_2OH$ or $-CH_2N(CH_3)_2$ when X is $-SCH_3$ and X' is H;

(B) when V and Y are N, Z is CH, R^4 is ethyl, R^5 is iso-propyl, X is Br, X' is H, and

(1) R^1 is CH_3, then
(a) R^3 can not be OH, piperazin-1-yl, $-CH_2$-piperidin-1-yl, $-CH_2$-(N-4-methylpiperazi n-1-yl), $-C(O)NH$-phenyl, $-CO_2H$, $-CH_2O$-(4-pyridyl), $-C(O)NH_2$, 2-indolyl, $-CH_2O$-(4-carboxyphenyl), $-N(CH_2CH_3)$(2-bromo-4-isopropylphenyl);
(2) R^2 is $-CH_2CH_2CH_3$ then R^3 can not be $-CH_2CH_2CH_3$

(C) when V, Y and Z are N, R^4 is ethyl, and

(1) R^5 is iso-propyl, X is bromo, and X' is H, then

(a) R^3 can not be OH or $-OCH_2CN$ when R^1 is CH_3 and
(b) R^3 can not be $-N(CH_3)_2$ when R^1 is $-N(CH_3)_2$;

(2) R^5 is $-OCH_3$, X is $-OCH_3$, and X' is H, then R^3 and R^1 can not both be chloro;
further provided that when J, K, and L are all CH and M is CR^5, then

(D) at least one of V, Y, and Z must be N;
(E) when V is CR^{1a}, Z and Y can not both be N;
(F) when Y is CR^{3a}, Z and V can not both be N;
(G) when Z is CR^2, V and Y must both be N;
(H) Z can be N only when both V and Y are N or when V is CR^{1a} and Y is CR^{3a};
(I) when V and Y are N, Z is CR^2, and R^2 is H or C_1-C_3 alkyl, and R^4 is C_1-C_3 alkyl, R^3 can not be 2-pyridinyl, indolyl, indolinyl, imidazolyl, 3-pyridinyl, 4-pyridinyl, 2-rnethyl-3-pyridinyl, 4-methyl-3-pyridinyl, furanyl, 5-methyl-2-furanyl, 2,5-dimethyl-3-furanyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-phenothiazinyl, or 4-pyrazinyl;
(J) when V and Y are N; Z is CR^2; R^2 is H or C_1-C_3 alkyl; R^4 is C_1-C_4 alkyl, R^5, X, and/or X' are OH, halo, CF_3, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, cyano, amino, carbamoyl, or C_1-C_4 alkanoyl; and R^1 is C_1-C_4 alkyl, then R^4 can not be -NH(substituted phenyl) or -N(C_1-C_4 alkyl) (substituted phenyl);

and wherein, when Y is CR^{29}:
J, K, L, M, Z, A, k, m, n, p, q, r, t, w, R^3, R^{10}, R^{11}, R^{12}, R^{13}, R^{16}, R^{18}, R^{19}, R^{21}, R^{23}, R^{24}, R^{25}, and R^{27} are as defined above and R^{25a}, in addition to being as defined above, can also be C_1-C_4 alkyl, but
V is N;
R^1 is C_1-C_2 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_2-C_4 alkoxy, halogen, amino, methylamino, dimethylamino, aminomethyl, or N-methylaminomethyl;
R^2 is independently selected at each occurrence from the group consisting of hydrogen, halo, C_1-C_3, alkyl, nitro, amino, and -CO_2R^{10};
R_4 is taken together with R^{29} to form a 5-membered ring and is -C(R^{26}) = or -N= when R^{29} is -C(R^{30})= or -N=, or -CH(R^{26})- when R^{29} is -CH(R^{30})-;
X is Cl, Br, I, S(O)nR^8, OR^8, halomethyl, -(CHR^{16})$_p$OR^8, cyano, -(CHR^{16})$_p$N$R^{14}R^{15}$, C(=O)R^8, C_1-C_6 alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10}, alkoxy, aryl-(C_1-C_{10})-alkyl, C_3-C_6 cycloalkyl, aryl-(C_1-C_{13})-alkoxy, nitro, thio-(C_1-C_{10})-alkyl, -C(=NOR^{16})-C_1-C_4-alkyl, -C(=NOR^{16})H, or C(=O)NR$^{14}R^{15}$ where substitution by R^{18} can occur on any carbon containing substituents;
X' is hydrogen, Cl, Br, I, S(O)$_n$$R^8$, -(CHR^{16})$_pOR^8$, halomethyl, cyano, -(CHR^{16})$_p$N$R^{14}R^{15}$, C(=O)R^8, C_1-C_6 alkyl, C_2-C_{10}alkenyl, C_2-C_{10}, alkynyl, C_1-C_{10} alkoxy, aryl-(C_1-C_{10})-alkyl, C_3-C_6 cycloalkyl, aryl-(C_2-C_{10})-alkoxy, nitro, thio-(C_2-C_{10})-alkyl, -C(=NOR^{16})-C_1-C_4-alkyl, -C(=NOR^{16})H, or C(=O)NR^{6}R^{15} where substitution by R^{18} can occur on any carbon containing substituents;
R^5 is halo, -C(=NOR^{16})-C_1-C_4-alkyl, C_1-C_6 alkyl, C_1-C_3 haloalkyl, C_1-C_6 alkoxy, (CHR^{16})$_p$OR^5, (CHR^{16})$_p$S(O)$_n$$R^8$, (CHR^{16})$_pNR^{14}R^{15}$, C_3-C_6 cycloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, aryl-(C_2-C_{10})-alkyl, aryl-(C_1-C_{10})-alkoxy, cyano, C_3-C_6 cycloalkoxy, nitro, amino-(C_1-C_{10})-alkyl, thio-(C_1-C_{10})-alkyl, SO_n(R^8), C(=O)R^8, -C(=NOR^{16})H, or C(=O)NR^{8}R^{15} where substitution by R^{18} can occur on any carbon containing substituents;
R^6 and R^7 are independently selected at each occurrence from the group consisting of hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, -(CH_2)$_k$$R^{13}$, ($C_4$-$C_{12}$)-cycloalkylalkyl, C_1-C_6 alkoxy, -(C_1-C_6 alkyl)-aryl, heteroaryl, aryl, -S(O_2)-aryl or -(C_1-C_6 alkyl)-heteroaryl or aryl wherein the aryl or heteroaryl groups are optionally substituted with 1-3 groups selected from hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, NHC(=O)(C_1-C_6 alkyl), NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, nitro, carboxy, CO_2(C_1-C_6 alkyl), and cyano; or can be taken together to form -(CH_2)$_q$A(CH_2)$_r$-, optionally substituted with 0-3 R^{17}; or, when considered with the commonly attached nitrogen, can be taken together to form a heterocycle, said heterocycle being substituted or carbon with 1-3 groups consisting of hydrogen, C_1-C_6 alkyl, hydroxy, or C_1-C_6 alkoxy;
R^8 is independently selected at each occurrence from the group consisting of hydrogen, C_1-C_6 alkyl, -(C_4-C_{12}) cycloalkylalkyl, (CH_2)$_k$$R^{22}$, C_3-C_{10} cycloalkyl, -(C_1-C_6 alkyl)-aryl, heteroaryl, -NR^{16}, -N(CH_2)$_m$NR^6R^7; -(CH_2)$_k$$R^{25}$, -($C_1$-$C_6$ alkyl)-heteroaryl or aryl optionally substituted with 1-3 groups selected from hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, NHC(=O)(C_1-C_6 alkyl), NH(C_1-C_6 alky'), N(C_1-C_6alkyl)$_2$, nitro, carboxy, CO_2(C_1-C_6 alkyl), and cyano;
R^9 is independently selected at each occurrence from R^{10}, hydroxy, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, C_2-C_4 alkenyl, and aryl substituted with 0-3 R^{18};
R^{14} and R^{15} are independently selected at each occurrence from the group consisting of hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, (CH_2)$_k$$R^{22}$, and aryl substituted with 0-3 R^{18};
R^{17} is independently selected at each occurrence from the group consisting of R^{10}, C_1-C_4 alkoxy, halo, OR^{23}, SR^{23}, and N$R^{23}R^{24}$;
R^{20} is independently selected at each occurrence from the group consisting of R^{10} and C(=O)R^{31};
R^{22} is independently selected at each occurrence from the group consisting of cyano, OR^{24}, SR^{24}, N$R^{23}R^{24}$, C_3-C_6 cycloalkyl, -S(O)$_n$$R^{31}$, and -C(=O)$R^{25}$;
R^{26} is hydrogen or halogen;
R^{28} is C_1-C_2, alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, hydrogen, C_1-C_2 alkoxy, halogen, or C_2-C_4 alkylamino;

R^{29} is taken together with R^4 to form a five membered ring and is: -CH(R^{30})-when R^4 is -CH(R^{28})-, -C(R^{30}) = or -N = when R^4 is -C(R^{28}) = or -N=;

R^{30} is hydrogen, cyano, C_1-C_2 alkyl, C_1-C_2 alkoxy, halogen, C_1-C_2 alkenyl, nitro, amido, carboxy, or amino;

R^{31} is C_1-C_4 alkyl, C_3-C_7 cycloalkyl, or aryl-(C_1-C_4) alkyl; provided that when J, K, and L are all CH, M is CR^5, Z is CH, R^3 is CH_3, R^{28} is H, R^5 is isopropyl, X is Br, X' is H, and R^1 is CH_3, then R^{30} can not be H, $-CO_2H$, or $-CH_2NH_2$; and further provided that when J, K and L are all CH; M is CR^5; Z is N; and

(A) R^{29} is -C(R^{30})=; then one of R^{28} or R^{30} is hydrogen;

(B) R^{29} is N; then R^3 is not halo, NH_2, NO_2, CF_3, CO_2H, CO_2-alkyl, alkyl, acyl, alkoxy, OH, or -(CH_2)$_m$Oalkyl;

(C) R^{29} is N; then R^{28} is not methyl if X or X' are bromo or methyl and R^5 is nitro; or

(D) R^{29} is N; and R^1 is CH_3; and R^3 is amino; then R^5 is not halogen or methyl.

[0026] Preferred compounds of this group include those wherein:

i) V is N, R^1 is methyl; and R^3 is aryl, NR^6R^7, or OR^8;

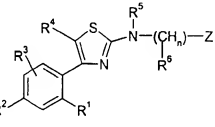
ii) V is N, R^1 is methyl; R^3 is aryl, NR^6R^7, or OR^8; and R^4 is methyl or ethyl;

iii) V is N, R^1 is methyl; R^3 is aryl, NR^6R^7, or OR^8; R^4 is methyl or ethyl; and X is O(C_1-C_6 alkyl), Br, or C_1-C_4 alkyl;

iv) V is N, R^1 is methyl; R^3 is aryl, NR^6R^7, or OR^8; R^4 is methyl, ethyl; X is OMe, Br, or (C_1-C_4 alkyl), M is C_1-C_4 alkyl, Br, Cl, or O(C_1-C_4 alkyl); and

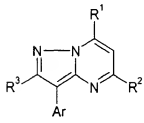
v) V is N, R^1 is methyl; R^3 is aryl, NR^6R^7, OR^8; or R^4 is methyl, ethyl; X is OMe, Br, or C_1-C_4 alkyl, M is C_1-C_4 alkyl, Br, Cl, or O(C_1-C_4 alkyl); and L is CH, or N.

X. The present invention also encompasses use of aminothiazole derivatives of the following formula, disclosed in WO 97/00868:



wherein each of R^1 and R^2 is independently a halogen atom; a C_1-C_5 hydroxyalkyl radical; C_1-C_5 alkyl; C_7-C_{10} aralkyl; C_1-C_5 alkoxy; trifluoromethyl; nitro; nitrile; a group -SR where R is hydrogen, a C_1-C_5 alkyl radical or a C_7-C_{10} aralkyl radical; a group S-CO-R where R is a C_1-C_5 alkyl radical or aralkyl in which the aryl portion is C_6-C_8 and the alkyl portion is C_1-C_4; a group -COOR' where R' is hydrogen or C_1-C_5 alkyl; a group -CONR'R" where R' and R" are as defined above for R'; a group -NR'R" where R' and R" are as previously defined for R'; a group-CONRaRb or NRaRb, where Ra and Rb, taken together with the nitrogen atom to which they are attached, form a 5- to 7-membered heterocyclic ring; or a group-NHCO-NR'R", where R' and R" are as defined above for R'; R^3 is hydrogen or as defined for R^1 and R^2 is a hydrogen atom; C_{1-5} alkyl; halogen; a hydroxymethyl group; or a formyl group; R^8 is C_1-C_5 alkyl; a C_3-C_7 cycloalkyl group; a cycloalkylalkyl group in which the cycloalkyl portion is C_3-C_7 and the alkyl portion is C_1-C_5; or C_5-C_6 alkenyl; n is 0 or 1; R^6 is C_{1-5} alkyl; alkoxyalkyl in which the alkyl portions are C_1-C_5; C_3-C_7 cycloalkyl; a cycloalkylalkyl group in which the cycloalkyl portion is C_3-C_7 and the alkyl portion is C_1-C_5; a cycloalkyloxyalkyl radical in which the cycloalkyl is C_3-C_7 and the alkyl is C_1-C_4; a hydroxyalkyloxyalkyl radical in which the alkyls are C_2-C_{10}; or an alkoxyalkyloxyalkyl radical in which the alkyls are C_3-C_{12}; and Z is an optionally substituted bi- or tricyclic aromatic or heteroaromatic group; and stereoisomers and/or addition salts thereof.

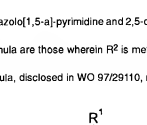
XI. CRF antagonists of the following formula, disclosed in WO 97/29109, may also be employed:



including the stereoisomers and the pharmaceutically acceptable acio addition salt forms thereof, wherein

R^1 is NR^4R^5 or OR^5;
R^2 is C_1-C_6alkyl, C_1-C_6alkyloxy or C_1-C_6alkylthio,
R^3 is hydrogen, C_1-C_6alkyl, C_1-C_6alkylsulfonyl, C_1-C_6alkylsulfoxy or C_1-C_6alkylthio;
R^4 is hydrogen, C_1-C_6alkyl, mono- or di(C_3-C_6cycloalkylmethyl, C_3-C_6cycloalkyl, C_3-C_6alkenyl, hydroxyC_1-C_6alkyl, C_1-C_6alkylcarbonyloxyC_1-C_6alkyl or C_1-C_6alkyloxyC_1-C_6alkyl;
R^5 is C_1-C_8alkyl, mono- or di(C_3-C_6cycloalkyl)methyl, Ar^1CH^2, C_3-C_6alkenyl, C_1-C_6alkyloxyC_1-C_6alkyl, hydroxyC_1-C_6alkyl, thienylmethyl, furanylmethyl, C_1-C_6alkylthioC_1-C_6alkyl, morpholinyl, mono- or di(C_1-C_6alkyl)aminoC_1-C_6alkyl, di(C_1-C_6alkyl)amino, C_1-C_6alkylcarbonylC_1-C_6alkyl, C_1-C_6alkyl substituted with imidazolyl; or a radical of formula -Alk-O-CO-Ar^1;
or R^4 and R^5 taken together with the nitrogen atom to which they are attached may form a pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group, optionally substituted with C_1-C_6alkyl or C_1-C_6alkyloxyC_1-C_6alkyl; and

[0027] Ar is phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from halo, C_1-C_6alkyl, trifluoromethyl, hydroxy, cyano, C_1-C_6alkyloxy, benzyloxy, C_1-C_6alkylthio, nitro, amino and mono- or di(C_1-C_6alkyl) amino; pyridinyl; pyridinyl substituted with 1 ~ 2 or 3 substituents independently selected from halo, C_1-C_6alkyl, trifluoromethyl, hydroxy, cyano, C_1-C_6alkyloxy, benzyloxy, C_1-C_6alkylthio, nitro, amino, mono- or di(C_1-C_6alkyl)amino and piperidinyl; and wherein said substituted phenyl may optionally be further substituted with one or more halogens;
[0028] Ar^1 is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C_1-C_6alkyl, C_1-C_6alkyloxy, di(C_1-C_6alkyl)aminoC_1-C_6alkyl, trifluoromethyl and C_1-C_6alkyl substituted with morpholinyl; or pyridinyl; and
Alk is C_1-C_6alkanediyl;
with the proviso that
5-methyl-3-phenyl-7-(phenylmethoxy)-pyrazolo[1,5-a]-pyrimidine and 2,5-dimethyl-7-(methylamino)-3-phenyl-pyrazolo[1,5-a]pyrimidine are not included.
[0029] Preferred compounds of this formula are those wherein R^2 is methyl; R^3 is hydrogen, or C_1-C_6 alkyl; and Ar is substituted phenyl or 3-pyridyl.
XII. CRF antagonists of the following formula, disclosed in WO 97/29110, may also be employed:



including the stereoisomers and the pharmaceutically acceptable acid addition salt forms thereof, wherein

X is S, SO or SO_2;
R^1 is NR^4R^5 or OR^5;
R^2 is C_1-C_6alkyl, C_1-C_6alkyloxy or C_1-C_6alkylthio;
R^3 is hydrogen, C_1-C_6alkyl, C_1-C_6alkylsulfonyl, C_1-C_6alkylsulfoxy or C_1-C_6alkylthio;

R^4 is hydrogen, C_{1-6}alkyl, mono- or di(C_3-C_6cycloalkyl)methyl, C_3-C_6cycloalkyl, C_3-C_6alkenyl, hydroxyC_1-C_6alkyl, C_1-C_6alkylcarbonyloxyC_1-C_6alkyl or C_1-C_6alkyloxyC_1-C_6alkyl;
R^5 is C_1-C_8alkyl, mono- or di(C_3-C_6cycloalkyl)methyl, Ar^1CH_2, C_3-C_6alkenyl, C_1-C_6alkyloxyC_1-C_6alkyl, hydroxyC_1-C_6alkyl, thienylmethyl, furanylmethyl, C_1-C_6alkylthioC_1-C_6alkyl, morpholinyl, mono- or di(C_1-C_6alkyl)aminoC_1-C_6alkyl, di(C_1-C_6alkyl)amino, C_1-C_6alkylcarbonylC_1-C_6alkyl, C_1-C_6alkyl substituted with imidazolyl; or a radical of formula -Alk-O-CO-Ar I;
or R^4 and R^5 taken together with the nitrogen atom to which they are attached may form a pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group, optionally substituted with C_1-C_6alkyl or C_1-C_6alkyloxyC_1-C_6alkyl;

[0030] Ar is phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from halo, C_1-C_6alkyl, trifluoromethyl, hydroxy, cyano, C_1-C_6alkyloxy, benzyloxy, C_1-C_6alkylthio, nitro, amino and mono- or di(C_1-C_6alkyl) amino; pyridinyl; pyridinyl substituted with 1, 2 or 3 substituents independently selected from halo, C_1-C_6alkyl, trifluoromethyl, hydroxy, cyano, C_1-C_6alkyloxy, benzyloxy, C_1-C_6alkylthio, nitro, amino, mono- or di(C_1-C_6alkyl)amino and piperidinyl; and wherein said substituted phenyl may optionally be further substituted with one or more halogens;

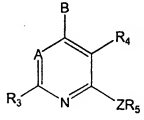
[0031] $Ar^1$is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C_1-C_6alkyl, C_1-C_6alkyloxy, di(C_1-C_6alkyl)aminoC_1-C_6alkyl trifluoromethyl, and C_1-C_6alkyl substituted with morpholinyl; or pyridinyl; and

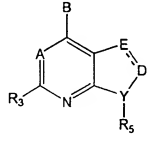
[0032] Alk is C_1-C_6alkanediyl.

[0033] Preferred compounds of this group include those wherein:

i) R^2 is methyl;
ii) R^2 is methyl, and Ar is substituted phenyl or 3-pyridyl;
iii) R^2 is methyl; R^3 is methyl; and Ar is substituted phenyl or 3-pyridyl

XIII. CRF antagonists of the following formula, disclosed in EP **0773023**, may also be employed:





or a pharmaceutically acceptable salt thereof, wherein

the dashed line represents an optional double bond;
A is $-CR_7$ or N;
B is $-NR_1R_2$, $-CR_1R_2R_{11}$, $-C(=CR_1R_{12})R_2$, $-NHCR_{11}R_1R_2$, $-OCR_{11}R_1R_2$, $-SCR_{11}R_1R_2$, $-CR_{11}R_2OR_1$, $-CR_{11}R_2SR_1$, $-C(S)R_2$, $-NHNR_1R_2$, $-CR_2R_{11}NHR_1$ or $-C(O)R_2$;
D is N or $-CR_{10}$ when a double bond connects E and D and E is $-CR_4$; $-CR_{10}$ when a double bond connects E and D and E is N; or $-CR_8R_9$, $-CHR_{10}$, -C=O, -C=S, -C=NH, or -C=NCH_3 when a single bond connects E and D;
E is $-CR_4$ or N when a double bond connects E and D, and E is $-CR_4R_6$ or $-NR_6$ when a single bond connects E and D;
Y is N or -CH;
Z is NH, O, S, $-N(C_1$-C_2 alkyl), or $-CR_{12}R_{13}$, wherein R_{12} and R_{13} are each, independently, hydrogen, trifluoromethyl, or methyl, or one of R_{12} and R_{13} is cyano and the other is hydrogen or methyl;
R_1 is hydrogen or C_1-C_6 alkyl which is optionally substituted with up to two substituents independently selected from hydroxy, cyano, nitro, fluoro, chloro, bromo, iodo, CF_3, C_1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), $-CO_2$(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), (C_1-C_4 alkyl)sulfinyl, (C_1-C_4 alkyl)sulfonyl, and (C_1-C_4 alkyl)sulfanyl, and wherein said C_1-C_6 alkyl, C_1-C_4 alkoxy, and C_1-C_4 alkyl moieties in the foregoing R_1 groups optionally contain one

double or triple bond;

R_2 is C_1-C_6 alkyl, heteroaryl, aryl, heteroaryl (C_1-C_4 alkyl), or aryl (C_1-C_4 alkyl), wherein said aryl and the aryl moiety of said (aryl)C_1-C_4 alkyl are selected from the group consisting of phenyl and naphthyl, and said heteroaryl and the heteroaryl moiety of said (heteroaryl)C_1-C_4 alkyl is selected from the group consisting of thienyl, benzothienyl, pyridyl, thiazolyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, and benzoxazolyl; or R^2 is C_3-C_8 cycloalkyl or (C_3-C_8 cycloalkyl)C_1-C_6 alkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said (C_3-C_8 cycloalkyl)C_1-C_6 alkyl having at least 4 ring members is optionally replaced by an oxygen or sulfur atom or by $-NR_{14}$ wherein R_{14} is hydrogen or C_1-C_4 alkyl, and wherein each of the foregoing R_2 groups is optionally substituted by up to three substituents independently selected from chloro, fluoro, and C_1-C_4 alkyl, or by one substituent selected from bromo, iodo, cyano, nitro, C_1-C_6 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), $-CO_2$(C_1-C_4 alkyl), (C_1-C_4 alkyl)sulfanyl, (C_1-C_4 alkyl)sulfinyl, and (C_1-C_4 alkyl)sulfonyl, and wherein said C_1-C_4 alkyl and C_1-C_6 alkyl moieties of the foregoing R_2 groups optionally contain one carbon-carbon double or triple bond;

or R^1 and R^2 of said $-NR_1R_2$ and said $-CR_1R_2R_{11}$ are taken together to form a saturated or partially saturated 5- to 8-membered ring, wherein said ring optionally contains one or two carbon-carbon double bonds, and wherein one or two of the ring carbons is optionally replaced by a heteroatom selected from O, S, and N;

R_3 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, SH, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), $-CH_2OH$, $-CH_2OCH_3$, -O(C_1-C_4 alkyl), (C_1-C_4 alkyl)sulfanyl, (C_1-C_4 alkyl)sulfonyl, or (C_1-C_4 alkyl) sulfinyl, wherein said C_1-C_6 alkyl and C_1-C_4 alkyl moieties of the foregoing R_3 groups optionally contain one double or triple bond and are optionally substituted by from one to three substituents independently selected from hydroxy, amino, C_1-C_3 alkoxy, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)$_2$, -NHCOCH$_3$, fluoro, chloro, and C_1-C_3 thioalkyl;

R_4 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, formyl, trifluoromethoxy, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_3$, $-CH_2CF_3$, CF_3, amino, nitro, -NH(C_1-C_4 alkyl), -N(CH_3)$_2$, -NHCOCH$_3$, -NHCONHCH$_3$, (C_1-C_4 alkyl)sulfanyl, (C_1-C_4 alkyl)sulfinyl, (C_1-C_4 alkyl)sulfonyl, cyano, hydroxy, -CO(C_1-C_4 alkyl), -CHO, or $-CO_2$(C_1-C_4 alkyl), wherein said C_1-C_6 alkyl, C_1-C_6 alkoxy, and C_1-C_4 alkyl moieties of the foregoing R_4 groups optionally contain one double or triple bond and are optionally substituted with one substituent selected from hydroxy, amino, -NHCOCH$_3$, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)$_2$, $-CO_2$(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), C_1-C_3 alkoxy, (C_1-C_3 alkyl)sulfanyl, fluoro, chloro, cyano, and nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, pyridinyl, tetrazolyl, or a 3- to 8-membered cycloalkyl ring or a 9- to 12-membered bicycloalkyl ring system, wherein said cycloalkyl ring and said bicycloalkyl ring system optionally contain one or two of O, S, or -N-G wherein G is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl, or benzyl, wherein each of the above R_5 groups is optionally substituted by up to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl, C_1-C_6 alkoxy, and trifluoromethyl, or one substituent selected from bromo, iodo, cyano, nitro, amino, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), $-CO_2$(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), $-SO_2NH$(C_1-C_4 alkyl),$-SO_2$N(C_1-C_4 alkyl)(C_1-C_2 alkyl), $-SO_2NH_2$, $-NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), and-SO_2(C_1-C_4 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl moieties of the foregoing R_5 groups optionally contain one double or triple bond and are optionally substituted by one or two substituents independently selected from fluoro, chloro, hydroxy, amino, methylamino, dimethylamino, and acetyl;

R_6 is hydrogen or C_1-C_6 alkyl, wherein said C_1-C_6 alkyl is optionally substituted by a single hydroxy, methoxy, ethoxy, or fluoro group;

R_7 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, C_1-C_4 alkoxy, -CO(C_1-C_4 alkyl), $-CO_2$ (C_1-C_4 alkyl), -OCF$_3$, CF$_3$, -CH$_2$OH, $-CH_2OCH_3$, or $-CH_2OCH_2CH_3$;

R_8 and R_9 are each, independently, hydrogen, hydroxy, methyl, ethyl, methoxy, or ethoxy;

or R_8 and R_9 together form an oxo (=O) group;

R_{10} is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, formyl, amino, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), cyano, carboxy, amido, or-SO_n(C_1-C_4 alkyl) wherein n is 0, 1, or 2, wherein said C_1-C_6 alkyl and C_1-C_4 alkyl moieties of the foregoing R_{10} groups are optionally substituted by one of hydroxy, trifluoromethyl, amino, carboxy, amido, -NHCO(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), $-CO_2$(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano, or nitro; and

R_{11} is hydrogen, hydroxy, fluoro, or methoxy.

[0034] Specific CRF antagonists useful in the practice of the present invention, include, without limitation, the following compounds:

4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-pyridine;
butyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]-ethyl-amine;
4-(butyl-ethylamino)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one;
4-(1-ethylpropoxy)-2,5-dimethyl-6-(2,4,6-trimethylphenoxy)-pyrimidine;
N-butyl-N-ethyl-2,5-dimethyl-NN-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine;
[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yl]-(2,4,6-trimethylphenyl)-amine;
6-(ethyl-propyl-amino)-2,7-dimethyl-9-(2,4,6-trimethylphenyl)-7,9-dihydro-purin-8-one;
3-[(4-methyl-benzyl)-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino]-propan-1-ol;
diethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
2-[butyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino]-ethanol;
dibutyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
butyl-ethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
butyl-ethyl-[6-methyl-3-methylsulfonyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
butyl-cyclopropylmethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1 H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
di-1-propyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
diallyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
butyl-ethyl-[6-chloro-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
butyl-ethyl-[6-methoxy-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
propyl-ethyl-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
4-(1-ethyl-propyl)-6-methyl-3-methylsulfanyl-1-(2,4,6-trimethylphenyl)-1 H-pyrazolo[3,4-d]pyrimidine;
n-butyl-ethyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
di-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
ethyl-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
diethyl-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
n-butyl-ethyl-[2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
2-[N-n-butyl-N-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-ethanol;
4-(1-ethyl-propyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine;
n-butyl-ethyl-[2,5-dimethyl-7-(2,4-dimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidyl-4-yl]-(1-ethyl-propyl)amine;
butyl-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl]-ethylamine;
[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4,b]pyridin-4-yl]-(1-methoxymethylpropyl)-amine;
4-(1-methoxymethylpropoxy)-3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridine;
(1-ethylpropyl)-[3,5,6-trimethyl-1-(2,4,6-trimethylphenyl)-1 H-pyrazolo[3,4-b]pyridin-4-yl]-amine;
4-(1-ethylpropoxy)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-b]pyridine;
4-(1-ethylpropoxy)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-b]pyridine;
4-(1-ethylpropoxy)-2,5-dimethyl-7-(2,6-dimethyl-4-bromophenyl)-7H-pyrrolo[2,3-b]pyridine;
2,5,6-trimethyl-7-(1-propylbutyl)-4-(2,4,6-trimethylphenoxy)-7H-pyrrolo[2,3-d]pyrimidine;
1 -(1 -ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenylamino)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
9-(1-ethylpropyl)-2-methyl-6-(2,4,6-trimethylphenylamino)-7,9-dihydro-purin-8-one;
1-(1-ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenoxy)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
1 -(1 -ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenoxy)-1H-imidazo[4,5-c]pyridine;
1 -(1 -ethylpropyl)-3,6-dimethyl-4-(2,4,6-trimethylphenoxy)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
1 -(1 -ethylpropyl)-3,6-dimethyl-4-(2,4,6-trimethylphenylamino)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
1 -(1 -ethyl-propyl)-4,7-dimethyl-5-(2,4,6-trimethyl-phenoxy)-1,4-dihydro-2H-pyrido[3,4-b]pyrazin-3-one;
1 -(1 -ethyl-propyl)-4,7-dimethyl-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetrahydro-pyrido[3,4-b]pyrazine;
1-(1-ethyl-propyl)-7-methyl-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetrahydro-pyrido[3,4-b]pyrazine;
1-(1-ethyl-propyl)-7-methyl-2-oxo-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetra-hydro-[1,6]naphthyridine-3-carboxylic acid methyl ester;
1-(1-ethyl-propyl)-7-methyl-2-oxo-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetra-hydro-[1,6]naphthyridine-3-carboxylic acid isopropyl ester;
1-(1-ethyl-propyl)-7-methyl-5-(2,4,6-trimethyl-phenoxy)-3,4-dihydro-1H-[1,6]naphthyridin-2-one;
1-(1-ethyl-propyl)-7-methyl-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetrahydro-[1,6]naphthyridine;
1-(1-ethyl-propyl)-7-methyl-5-(2,4,6-trimethyl-phenoxy)-1,4-dihydro-2H-3-oxa-1,6-diaza-naphthalene;
1-(1-ethyl-propyl)-4,7-dimethyl-5-(2,4,6-trimethyl-phenoxy)-1,4-dihydro-2H-3-oxa-1,6-diaza-naphthalene;
1-(1-ethyl-propyl)-3,7-dimethyl-5-(2,4,6-trimethyl-phenoxy)-3,4-dihydro-1 H-3-oxa-[1,6]-naphthyridin-2-one;
1-(1-ethyl-propyl)-3,3,6-trimethyl-4-(2,4,6-trimethyl-phenoxy)-2,3-dihydro-1 H-pyrrolo[3,2-c]pyridine;

7-(1-ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a] pyrimidine;
[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-(1-ethyl-propyl)-amine;
(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-amine;
7-(1-ethyl-propoxy)-2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidine;
[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-ethyl-propyl-amine;
[6-bromo-5-bromomethyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-(1-ethyl-propyl)-amine;
(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-amine;
[6-bromo-5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-(1-ethyl-propyl)-methyl-amine;
7-(1-ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridine;
4-(1-ethyl-propoxy)-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine;
(±)-2,5-dimethyl-4-(tetrahydro-furan-3-yloxy)-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo-[3,2-d]pyrimidine;
2,5-dimethyl-4-(S)-(tetrahydro-furan-3-yloxy)-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo-[3,2-d]pyrimidine;
2,5-dimethyl-4-(1-propyl-butoxy)-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine;
4-sec-butylsulfanyl-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine;
4-(butyl-ethyl-amino)-2,6-dimethyl-8-(2,4,6-trimethyl-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;
8-(1-ethyl-propoxy)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido[2,3-b] pyrazin-2-one;
8-(1-ethyl-propoxy)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido [2,3-b]pyrazine;
4-(1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;
5-(1-ethyl-propoxy)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;
5-(1-ethyl-propoxy)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,2-dihydro-3-oxa-1, 8-diaza-naphthalen-4-one;
8-(1-ethyl-propoxy)-1,6-dimethyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;
(1-ethyl-propyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-quinolin-4-yl]-amine;
4-(butyl-ethyl-amino)-2,6-dimethyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;
4-(butyl-ethyl-amino)-2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,8-dihydro-6H- pyrido[2,3-d]pyrimidin-7-one;
4-(1-ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,8-dihydro-6 H- pyrido[2,3-d]pyrimidin-7-one;
(butyl-ethyl)-[2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidin-4-yl]-amine;
(propyl-ethyl)-[2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidin-4-yl]-amine;
(diethyl)-[2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,6,7,8-tetrahydro-pyrido [2,3-d]pyrimidin-4-yl]-amine;
(1-ethyl-propyl)-[2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidin-4-yl]-amine;
(1-ethyl-propoxy)-2-methyl-8-(2,6-trimethyl-4-bromo-phenyl)-5,6,7,8-tetrahydro- pyrido[2,3-d]pyrimidine;
4-(butyl-ethyl-amino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;
4-(1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-5,8-dihydro-6H-pyrido [2,3-d]pyrimidin-7-one;
(butyl-ethyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2, 3-d] pyrimidin-4-yl]-amine;
(propyl-ethyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-pyrido-[2,3-d] pyrimidin-4-yl]-amine;
(diethyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d] pyrimidin-4-yl]-amine;
(1-ethyl-propyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d] pyrimidin-4-yl]-amine;
(1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d] pyrimidine;
8-(1-ethyl-propoxy)-6-methyl-4-(2,6-dimethyl-4-bromo-phenyl)-3,4-dihydro-1 H-pyrido [2,3-b]pyrazin-2-one;
8-(1-ethyl-propoxy)-6-methyl-4-(2,6-dimethyl-4-bromo-phenyl)-1,2,3,4-tetrahydro- pyrido[2,3-b]pyrazine;
4-(1-ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-quinoline;
5-(1-ethyl-propoxy)-7-methyl-1-(2,6-dimethyl-4-bromo-phenyl)-1,4-dihydro-2 H- 3-oxa-1,8-diaza-naphthalene;
5-(1-ethyl-propoxy)-7-methyl-1-(2,6-dimethyl-4-bromo-phenyl)-1,2-dihydro-3 - oxa-1,8-diaza-naphthalen-4-one;
8-(1-ethyl-propoxy)-1,6-dimethyl-4-(2,6-dimethyl-4-bromo-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;
(1-ethyl-propyl)-[2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-quinolin-4-yl]-amine;
4-(butyl-ethyl-amino)-2,6-dimethyl-8-(2,6-dimethyl-4-chloro-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;
8-(1-ethyl-propoxy)-6-methyl-4-(2,6-dimethyl-4-chloro-phenyl)-3,4-dihydro-1 H- pyrido[2,3-b]pyrazin-2-one;
8-(1-ethyl-propoxy)-6-methyl-4-(2,6-dimethyl-4-chloro-phenyl)-1,2,3,4-tetrahydro- pyrido[2,3-b]pyrazine;
4-(1-ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-chloro-phenyl)-quinoline;
5-(1-ethyl-propoxy)-7-methyl-1-(2,6-dimethyl-4-chloro-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;
5-(1-ethyl-propoxy)-7-methyl-1-(2,6-dimethyl-4-chloro-phenyl)-1,2-dihydro-3-oxa-1,8-diaza-naphthalen-4-one;
8-(1-ethyl-propoxy)-1,6-dimethyl-4-(2,6-dimethyl-4-chloro-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;
(1-ethyl-propyl)-[2-methyl-8-(2,6-dimethyl-4-chloro-phenyl)-quinolin-4-yl]-amine;
8-(1-hydroxymethyl-propoxy)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro - 1 H-pyrido[2,3-b]pyrazin-2-one;
8-(1-hydroxymethyl-propylamino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido[2,3-b]pyrazin-2-one;

8-(1-ethyl-propylamino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro- 1H-pyrido[2,3-b]pyrazin-2-one;
8-diethylamino-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido-[2,3-b] pyrazin-2-one;
8-(ethyl-propyl-amino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido[2,3-b]pyrazin-2-one;
8-(butyl-ethyl-amino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido [2,3-b]pyrazin-2-one;
8-(1-hydroxymethyl-propoxy)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;
8-(1-hydroxymethyl-propylamino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4 - tetrahydro-pyrido[2,3-b]pyrazine;
8-(1-ethyl-propylamino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;
8-diethylamino-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;
8-(ethyl-propyl-amino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro - pyrido[2,3-b]pyrazine;
8-(butyl-ethyl-amino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;
4-(1-hydroxymethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;
4-(1-hydroxymethyl-propylamino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;
4-(1-ethyl-propylamino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;
4-diethylamino-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;
4-(ethyl-propyl-amino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;
4-(butyl-ethyl-amino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;
5-(1-hydroxymethyl-propoxy)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro - 2H-3-oxa-1,8-diaza-naphthalene;
5-(1-hydroxymethyl-propylamino)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;
5-(1-ethyl-propylamino)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3- oxa-1,8-diaza-naphthalene;
5-d iethylamino-5-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-oxa-1,8 - diaza-naphthalene;
5-(ethyl-propyl-amino)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;
8-(butyl-ethyl-amino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;
4-(2,4-dichlorophenyl)-5-methyl-2-[N-(1-(methoxymethyl)-1-(naphth-2-yl) methyl)-N-propylamino]thiazole;
oxalate of 4-(2,4-dichlorophenyl)-5-methyl-2-[N-(6-methoxyisoquinol-5-yl)-N-propylamino]thiazole;
oxalate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(6-methylisoquinol-5 -yl)-N-propylamino]thiazole;
4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(1-methoxycarbonylmethylindol - 5-yl)-N-propylamino]thiazole;
oxalate of -(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(6-methoxyisoquinol-5-yl)-N-propylamino]thiazole;
oxalate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(6-chloroisoquinol-5 -yl)-N- propylamino]thiazole;
oxalate of -(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(6-methoxyisoquinol-5 -yl)-N- propylamino]thiazole;
4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-1-methoxynaphth-2-yl)-N-propylamino]thiazole;
oxalate of 4-(2-chloro-4-trifluoromethylphenyl)-5-methyl-2-[N-6-methoxyisoquinol-5-yl)-N-propylamino]thiazole;
chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(2-ethoxynaphth-1-yl)-N- propylamino]thiazole;
chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2[N-(2,3-dimethylnaphth-1-yl)-N-propylamino]thiazole;
chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(6-bromo-2-methoxynaphth-1-yl)-N-propylamino]thiazole;
chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(2,6-dimethylnaphth-1-yl)-N-propylamino]thiazole;
chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(1-(methoxymethyl)-1-(naphth-2-yl)methyl)-N-propylamino]thiazole;
chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(1-(cyclopropyl)-1-(naphth-2-yl)methyl)-N-propylamino]thiazole;
3-(2,4-dichlorophenyl)-5-methyl-7(N-propyl-N-cyclopropanemethylamino)pyrazolo[2,3-a]pyrimidine;
3-(2,4-dichlorophenyl)-5-methyl-7-(N-allyl-N-cyclopropanemethylamino)pyrazolo[2,3-a]pyrimidine;
2-methylthio-3-(2,4-dichlorophenyl)-5-methyl-7-(N,N-diallylamino)pyrazolo[2,3-a]pyrimidine;
2-methylthio-3-(2,4-dichlorophenyl)-5-methyl-7-(N-butyl-N-cyclopropane-methyl-amino)pyrazolo[2,3-a]pyrimidine;
2-methylthio-3-(2,4-dichlorophenyl)-5-methyl-7-(N-propyl-N-cyclopropane-methyl-amino)pyrazolo[2,3-a]pyrimidine;
2-methyl-3-(4-chlorophenyl)-5-methyl-7-(N,N-dipropylamino)-pyrazolo[2,3-a] pyrimidine;
3-[6-(dimethylamino)-3-pyridinyl-2,5-dimethyl-N,N-dipropylpyrazolo[2,3-a] pyrimidin-7-amine;
3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-N,N-dipropyl- pyrazolo[2,3-a]pyrimidine-7-amine;
3-(2,4-dimethoxyphenyl)-2,5-dimethyl-7-(N-propyl-N-methyloxyethylamino)pyrazolo(2,3-a)pyrimidine;
3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-N-propyl-N-cyclopropylmethyl-pyrazolo[2,3-a]pyrimidin-7-amine;
3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-N-ethyl-N-cyclopropylmethyl-pyrazolo[2,3-a]pyrimidin-7-amine;
7-(N-diethylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl-[1,5-a]-pyrazolopyrimidine;
7-(N-(3-cyanopropyl)-N-propylamino-2,5,dimethyl-3-(2,4-dimethylphenyl)-[1,5-a]-pyrazolopyrimidine;

[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-(1-ethyl-propyl)-amine;
[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-(1-ethyl-propyl)-amine;
cyclopropylmethyl-[3-(2,4-dimethyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-propyl-amine;
cyclopropylmethyl-[3-(2-methyl-4-chloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-propyl-amine;
cyclopropylmethyl-[3-(2,4-di-chloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-propyl-amine;
[3-(2-methyl-4-chloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-di-propyl-amine;
[2,5-dimethyl-3-(2,4-dimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-(1-ethyl-propyl)-amine;
[2,5-dimethyl-3-(2,4-dichloro-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-(1-ethyl-propyl)-amine; and
4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester.

[0035] Even more particularly, specific CRF antagonists useful in the practice of the present invention include, without limitation, the following compounds:

4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-pyridine;
4-(1-ethylpropoxy)-2,5-dimethyl-6-(2,4,6-trimethylphenoxy)-pyrimidine;
[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yl]-(2,4,6-trimethylphenyl)-amine;
3-{[4-methyl-benzyl)-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propan-1-ol;
propyl-ethyl-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
ethyl-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
2-{N-n-butyl-N-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}-ethanol;
[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4,b]pyridin-4-yl]-(1-methoxymethylpropyl)-amine;
4-(1-ethylpropoxy)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-b]pyridine;
2,5,6-trimethyl-7-(1-propylbutyl)-4-(2,4,6-trimethylphenoxy)-7H-pyrrolo[2,3-d]pyrimidine;
1-(1-ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenoxy)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
1 -(1 -ethyl-propyl)-4,7-dimethyl-5-(2,4,6-trimethyl-phenoxy)-1,4-dihydro-2H-pyrido[3,4-b]pyrazin-3-one;
1 -(1 -ethyl-propyl)-4,7-dimethyl-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetrahydro-pyrido[3,4-b]pyrazine;
1-(1-ethyl-propyl)-7-methyl-2-oxo-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetra-hydro-[1,6]naphthyridine-3-carboxylic acid isopropyl ester;
1 -(1 -ethyl-propyl)-7-methyl-5-(2,4,6-trimethyl-phenoxy)-1,4-dihydro-2H-3-oxa-1,6-diaza-naphthalene;
(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-amine;
7-(1-ethyl-propoxy)-2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidine;
4-(1-ethyl-propoxy)-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine;
4-(butyl-ethyl-amino)-2,6-dimethyl-8-(2,4,6-trimethyl-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;
8-(1-ethyl-propoxy)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido [2,3-b]pyrazine;
4-(1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;
(1-ethyl-propyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-quinolin-4-yl]-amine;
(propyl-ethyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-pyrido-[2,3-d] pyrimidin-4-yl]-amine;
(1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d] pyrimidine;
8-(1-hydroxymethyl-propylamino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1 H-pyrido[2,3-b]pyrazin-2-one;
4-(1-hydroxymethyl-propylamino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;
5-(1-hydroxymethyl-propylamino)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;
[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-(1-ethyl-propyl)-amine;
cyclopropylmethyl-[3-(2,4-dimethyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-propyl-amine;
[2,5-dimethyl-3-(2,4-dimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-(1-ethyl-propyl)-amine;
3-[6-(dimethylamino)-3-pyridinyl-2,5-dimethyl-N,N-dipropylpyrazolo[2,3-a] pyrimidin-7-amine;
3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-N,N-dipropyl-pyrazolo[2,3-a]pyrimidine-7-amine;
3-(2,4-dimethoxyphenyl)-2,5-dimethyl-7-(N-propyl-N-methyloxyethylamino)-pyrazolo(2,3-a)pyrimidine;
7-(N-diethylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl-[1,5-a]-pyrazolopyrimidine; and
7-(N-(3-cyanopropyl)-N-propylamino-2,5,dimethyl-3-(2,4-dimethylphenyl)-[1,5-a]-pyrazolopyrimidine.

[0036] Methods for making the CRF antagonists described above are disclosed in the above-listed patents and published patent applications incorporated by reference herein.

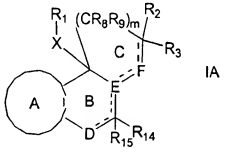
[0037] In one aspect of the present invention, a CRF antagonist may be used in combination with a GR antagonist. The glucocorticoid receptor (GR) is present in glucocorticoid responsive cells where it resides in the cytosol in an inactive state until it is stimulated by an agonist. Upon stimulation the glucocorticoid receptor translocates to the cell

nucleus where it specifically interacts with DNA and/or protein(s) and regulates transcription in a glucocorticoid responsive manner. Two examples of proteins that interact with the glucocorticoid receptor are the transcription factors, API and NFK-B. Such interactions result in inhibition of API- and NFκ-B- mediated transcription and are believed to be responsible for the antiinflammatory activity of endogenously administered glucocorticoids. In addition, glucocorticoids may also exert physiologic effects independent of nuclear transcription. Biologically relevant glucocorticoid receptor agonists include cortisol and corticosterone. Many synthetic glucocorticoid receptor agonists exist including dexamethasone, prednisone and prednisilone. As defined above, a glucocorticoid receptor (GR) antagonist refers to a compound that binds to the receptor and prevents a glucocorticoid receptor agonist from binding and eliciting GR mediated events, including transcription. RU486 is an example of a non-selective glucocorticoid receptor antagonist.

[0038] Any GR antagonist can be used to practice the present invention, including those that are described in commonly assigned International patent application, PCT/IB00/00366, filed 27 March 2000; U.S. Patent No. 5,696,127; International patent publications WO 99/41256 and WO 99/41257; U.S. Patent 5,696,127; European patent publication 188396; European patent publication 683172; International patent publication WO 98/26783; International patent publication WO 98/27986; International patent publication WO 98/31702; European patent publication 803146; and International patent publications WO 99/41256 and WO 99/41257. As noted above, the texts of all of these applications and publications are incorporated by reference herein in their entireties.

[0039] Following are listed particular examples of GR antagonists that may be used in practicing the present invention. It is understood that the variables, e.g., "A", "B", "R_1", "R_2", etc., employed in the generic formula IA below have the meanings attributed to them only with respect to that particular formula.

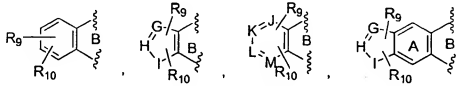
[0040] For example, the GR antagonists may be of the following structural formula IA, including the pharmaceutically acceptable salts thereof, as described in commonly assigned International patent application, PCT/IB00/00366, filed 27 March 2000:



IA

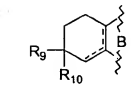
an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug;
wherein m is 1 or 2;

- - - represents an optional bond;
A is selected from the group consisting of



A-1 , A-2 , A-3 , A-4

and



A-5

D is CR_7, CR_7R_{16}, N, NR_7 or O;
E is C, CR_6 or N;
F is CR_4, CR_4R_5 or O;
G, H and I together with 2 carbon atoms from the A-ring or 2 carbon atoms from the B-ring form a 5-membered heterocyclic ring comprising one or more N, O or S atoms; provided that there is at most one of O and S per ring;
J, K, L and M together with 2 carbon atoms from the B-ring forms a 6-membered heterocyclic ring comprising 1 or more N atoms;
X is a) absent, b) $-CH_2-$, c) -CH(OH)- or d) -C(O)-;
R_1 is a) -H, b) $-Z\text{-}CF_3$, c) $-Z\text{-}(C_1\text{-}C_6)$alkyl, d) $-Z\text{-}(C_2\text{-}C_6)$alkenyl, e) $-Z\text{-}(C_2\text{-}C_6)$alkynyl, f) -CHO, g) -CH=N-OR_{12}, h) -Z-C(O)OR_{12}, i) -Z-C(O)-$NR_{12}R_{13}$, j) -Z-C(O)-NR_{12}-Z-het, k) -Z-$NR_{12}R_{13}$, l) -Z-NR_{12}het, m) -Z-het, n) -Z-O-het, o) -Z-aryl', p) -Z-O-aryl', q) -CHOH-aryl' or r) -C(O)-aryl' wherein aryl' in substituents o) to r) is substituted independently with 0, 1 or 2 of the following: -Z-OH, -Z-$NR_{12}R_{13}$, -Z-NR_{12}-het, -C(O)$NR_{12}R_{13}$, -C(O)O$(C_1\text{-}C_6)$alkyl, -C(O)OH, -C(O)-het, -NR_{12}-C(O)-$(C_1\text{-}C_6)$alkyl, -NR_{12}-C(O)-$(C_2\text{-}C_6)$alkenyl, -NR_{12}-C(O)-$(C_2\text{-}C_6)$alkynyl, -NR_{12}-C(O)-Z-het, -CN, -Z-het, -O-$(C_1\text{-}C_3)$alkyl-C(O)-$NR_{12}R_{13}$, -O-$(C_1\text{-}C_3)$alkyl-C(O)O$(C_1\text{-}C_6)$alkyl, -NR_{12}-Z-C(O)O$(C_1\text{-}C_6)$alkyl, -N(Z-C(O)O$(C_1\text{-}C_6)$alkyl$)_2$, -NR_{12}-Z-C(O)-$NR_{12}R_{13}$, -Z-NR_{12}-SO_2-R_{13}, -NR_{12}-SO_2-het, -C(O)H, -Z-NR_{12}-Z-O$(C_1\text{-}C_6)$alkyl, -Z-NR_{12}-Z-$NR_{12}R_{13}$, -Z-NR_{12}-$(C_3\text{-}C_6)$cycloalkyl, -Z-N(Z-O$(C_1\text{-}C_6)$alkyl$)_2$, -SO_2R_{12}, -SOR$_{12}$, -SR_{12}, -$SO_2NR_{12}R_{13}$, -O-C(O)-$(C_1\text{-}C_4)$alkyl, -O-SO_2-$(C_1\text{-}C_4)$alkyl, -halo or $-CF_3$;
Z for each occurrence is independently a) $-(C_0\text{-}C_6)$alkyl, b) $-(C_2\text{-}C_6)$alkenyl or c) $-(C_2\text{-}C_6)$alkynyl;
R_2 is a) -H, b) -halo, c) -OH, d) $-(C_1\text{-}C_6)$alkyl substituted with 0 or 1 -OH, e) -$NR_{12}R_{13}$, f) -Z-C(O)O$(C_1\text{-}C_6)$alkyl, g) -Z-C(O)$NR_{12}R_{13}$, h) -O-$(C_1\text{-}C_6)$alkyl, i) -Z-O-C(O)-$(C_1\text{-}C_6)$alkyl, j) -Z-O-$(C_1\text{-}C_3)$alkyl-C(O)-$NR_{12}R_{13}$, k) -Z-O-$(C_1\text{-}C_3)$alkyl-C(O)-O$(C_1\text{-}C_6)$alkyl, l) -O-$(C_2\text{-}C_6)$alkenyl, m) -O-$(C_2\text{-}C_6)$alkynyl, n) -O-Z-het, o) -COOH, p) -C(OH)$R_{12}R_{13}$ or q) -Z-CN;
R_3 is a) -H, b) $-(C_1\text{-}C_{10})$alkyl wherein 1 or 2 carbon atoms, other than the connecting carbon atom, may optionally be replaced with 1 or 2 heteroatoms independently selected from S, O and N and wherein each carbon atom is substituted with 0, 1 or 2 R_y, c) $-(C_2\text{-}C_{10})$alkenyl substituted with 0, 1 or 2 R_y, d) $-(C_2\text{-}C_{10})$alkynyl wherein 1 carbon atom, other than the connecting carbon atom, may optionally be replaced with 1 oxygen atom and wherein each carbon atom is substituted with 0, 1 or 2 R_y, e) -CH=C=CH_2, f) -CN, g) $-(C_3\text{-}C_6)$cycloalkyl, h) -Z-aryl, i) -Z-het, j) -C(O)O$(C_1\text{-}C_6)$alkyl, k) -O$(C_1\text{-}C_6)$alkyl, l) -Z-S-R_{12}, m) -Z-S(O)-R_{12}, n) -Z-$S(O)_2$-R_{12}, O) $-CF_3$ p) -NR_{12}-O-$(C_1\text{-}C_6)$ alkyl or q) $-CH_2OR_y$;
provided that one of R_2 and R_3 is absent when there is a double bond between CR_2R_3 (the 7 position) and the F moiety (the 8 position) of the C-ring;
R_y for each occurrence is independently a) -OH, b) -halo, c) $-Z\text{-}CF_3$, d) $-Z\text{-}CF(C_1\text{-}C_3\ alkyl)_2$, e) -CN, f) -$NR_{12}R_{13}$, g) $-(C_3\text{-}C_6)$cycloalkyl, h) $-(C_3\text{-}C_6)$cycloalkenyl, i) $-(C_0\text{-}C_3)$alkyl-aryl, j) -het or k) $-N_3$;
or R_2 and R_3 are taken together to form a) =CHR_{11}, b) =NOR_{11}, c) =O, d) =NR_{12}, e) =N-NR_{12}-C(O)-R_{12}, f) oxiranyl or g) 1,3-dioxolan-4-yl;
R_4 and R_5 for each occurrence are independently a) -H, b) -CN, c) $-(C_1\text{-}C_6)$alkyl substituted with 0 to 3 halo, d) $-(C_2\text{-}C_6)$alkenyl substituted with 0 to 3 halo, e) $-(C_2\text{-}C_6)$alkynyl substituted with 0 to 3 halo, f) -O-$(C_1\text{-}C_6)$alkyl substituted with 0 to 3 halo, g) -O-$(C_2\text{-}C_6)$alkenyl substituted with 0 to 3 halo, h) -O-$(C_2\text{-}C_6)$alkynyl substituted with 0 to 3 halo, i) halo, j) -OH, k) $-(C_3\text{-}C_6)$cycloalkyl or l) $(C_3\text{-}C_6)$cycloalkenyl;
or R_4 and R_5 are taken together to form =O;
R_6 is a) -H, b) -CN, c) $-(C_1\text{-}C_6)$alkyl substituted with 0 to 3 halo, d) $-(C_2\text{-}C_6)$alkenyl substituted with 0 to 3 halo, e) $-(C_2\text{-}C_6)$alkynyl substituted with 0 to 3 halo or f) -OH;
R_7 and R_{16} for each occurrence are independently a) -H, b) -halo, c) -CN, d) $-(C_1\text{-}C_6)$alkyl substituted with 0 to 3 halo, e) $-(C_2\text{-}C_6)$alkenyl substituted with 0 to 3 halo or f) $-(C_2\text{-}C_6)$alkynyl substituted with 0 to 3 halo; provided that R_7 is other than -CN or -halo when D is NR_7;
or R_7 and R_{16} are taken together to form =O;
R_8, R_9, R_{14} and R_{15} for each occurrence are independently a) -H, b) -halo, c) $(C_1\text{-}C_6)$alkyl substituted with 0 to 3 halo, d) $-(C_2\text{-}C_6)$alkenyl substituted with 0 to 3 halo, e) $-(C_2\text{-}C_6)$alkynyl substituted with 0 to 3 halo, f) -CN, g) $-(C_3\text{-}C_6)$cycloalkyl, h) $-(C_3\text{-}C_6)$cycloalkenyl, i) -OH, j) -O-$(C_1\text{-}C_6)$alkyl, k) -O-$(C_1\text{-}C_6)$alkenyl, l) -O-$(C_1\text{-}C_6)$alkynyl, m)

-$NR_{12}R_{13}$, n) -C(O)OR_{12} or o) -C(O)$NR_{12}R_{13}$;
or R_8 and Rg are taken together on the C-ring to form =O; provided that when m is 2, only one set of R_8 and R_9 are taken together to form =O;
or R_{14} and R_{15} are taken together to form =O; provided that when R_{14} and R_{15} are taken together to form =O, D is other than CR_7 and E is other than C;
R_{10} is a) -(C_1-C_{10})alkyl substituted with 0 to 3 substituents independently selected from -halo, -OH and -N_3, b) -(C_2-C_{10})alkenyl substituted with 0 to 3 substituents independently selected from -halo, -OH and -N_3, c) -(C_2-C_{10})alkynyl substituted with 0 to 3 substituents independently selected from -halo, -OH and -N_3, d) -halo, e) -Z-CN, f) -OH, g) -Z-het, h) -Z-$NR_{12}R_{13}$, i) -Z-C(O)-het, j) -Z-C(O)-(C_1-C_6)alkyl, k) -Z-C(O)-$NR_{12}R_{13}$, l) -Z-C(O)-NR_{12}-Z-CN, m) -Z-C(O)-NR_{12}-Z-het, n) -Z-C(O)-NR_{12}-Z-aryl, o) -Z-C(O)-NR_{12}-Z-$NR_{12}R_{13}$, p) -Z-C(O)-NR_{12}-Z-O(C_1-C_6)alkyl, q) -(C_2-C_6)alkyl-C(O)OH, r) -Z-C(O)O(C_1-C_6)alkyl, s) -Z-O-(C_2-C_6)alkyl-het, t) -Z-O-(C_2-C_6)alkyl-aryl, u) -Z-O-(C_1-C_6)alkyl substituted with 0 to 2 R_x, v) -Z-O-(C_1-C_6)alkyl-CH(O), w) -Z-O-(C_1-C_6)alkyl-NR_{12}-het, x) -Z-O-Z-het-Z-het, y) -Z-O-Z-het-Z-$NR_{12}R_{13}$, z) -Z-O-Z-het-C(O)-het, a1) -Z-O-Z-C(O)-het, b1) -Z-O-Z-C(O)-het-het, c1) -Z-O-Z-C(O)-(C_1-C_6)alkyl, d1) -Z-O-Z-C(S)-$NR_{12}R_{13}$, e1) -Z-O-Z-C(O)-$NR_{12}R_{13}$, f1) -Z-O-Z-(C_1-C_3)alkyl-C(O)-$NR_{12}R_{13}$, g1) -Z-O-Z-C(O)-O(C_1-C_6)alkyl, h1) -Z-O-Z-C(O)-OH, i1) -Z-O-Z-C(O)-NR_{12}-O(C_1-C_6)alkyl, j1) -Z-O-Z-C(O)-NR_{12}-OH, k1) -Z-O-Z-C(O)-NR_{12}-Z-$NR_{12}R_{13}$, l1) -Z-O-Z-C(O)-NR_{12}-Z-het, m1) -Z-O-Z-C(O)-NR_{12}-SO_2-(C_1-C_6)alkyl, n1) -Z-O-Z-C(=NR_{12})($NR_{12}R_{13}$), o1) -Z-O-Z-C(=NOR_{12})($NR_{12}R_{13}$), p1) -Z-NR_{12}-C(O)-O-Z-$NR_{12}R_{13}$, q1) -Z-S-C(O)-$NR_{12}R_{13}$, r1) -Z-O-SO_2-(C_1-C_6)alkyl, s1) -Z-O-SO_2-aryl, t1) -Z-O-SO_2-$NR_{12}R_{13}$, u1) -Z-O-SO_2-CF_3, v1) -Z-NR_{12}C(O)OR_{13} or w1) -Z-NR_{12}C(O)R_{13};
or Rg and R_{10} are taken together on the moiety of formula A-5 to form a) = O or b) = NOR_{12};
R_{11} is a) -H, b) (C_1-C_3)alkyl, c) -(C_2-C_6)cycloalkyl or d) -(C_0-C_3)alkyl-aryl;
R_{12} and R_{13} for each occurrence are each independently a) -H, b) -(C_1-C_6)alkyl wherein 1 or 2 carbon atoms, other than the connecting carbon atom, may optionally be replaced with 1 or 2 heteroatoms independently selected from S, O and N and wherein each carbon atom is substituted with 0 to 6 halo, c) -(C_2-C_6)alkenyl substituted with 0 to 6 halo or d) -(C_1-C_6)alkynyl wherein 1 carbon atom, other than the connecting carbon atom, may optionally be replaced with 1 oxygen atom and wherein each carbon atom is substituted with 0 to 6 halo;
or R_{12} and R_{13} are taken together with N to form het;
or R_8 and R_{14} or R_{15} are taken together to form 1,3-dioxolanyl;
aryl is a) phenyl substituted with 0 to 3 R_x, b) naphthyl substituted with 0 to 3 R_x or c) biphenyl substituted with 0 to 3 R_x;
het is a 5-,6- or 7-membered saturated, partially saturated or unsaturated ring containing from one (1) to three (3) heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another heterocycle; and the nitrogen may be in the oxidized state giving the N-oxide form; and substituted with 0 to 3 R_x;
R_x for each occurrence is independently a) -halo, b) -OH, c) -(C_1-C_6)alkyl, d) -(C_2-C_6)alkenyl, e) -(C_2-C_6)alkynyl, f) -O(C_1-C_6)alkyl, g) -O(C_2-C_6)alkenyl, h) -O(C_2-C_6)alkynyl, i) -(C_0-C_6)alkyl-$NR_{12}R_{13}$, j) -C(O)-$NR_{12}R_{13}$, k) -Z-SO_2R_{12}, l)-Z-SOR_{12}, m) -Z-SR_{12}, n) -NR_{12}-SO_2R_{13}, o) -NR_{12}-C(O)-R_{13}, p) -NR_{12}-OR_{13}, q) -SO_2-$NR_{12}R_{13}$, r) -CN, s) -CF_3, t) -C(O)(C_1-C_6)alkyl, u) =O, v) -Z-SO_2-phenyl or w) -Z-SO_2-het;
aryl' is phenyl, naphthyl or biphenyl;
het' is a 5-,6- or 7-membered saturated, partially saturated or unsaturated ring containing from one (1) to three (3) heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another heterocycle; provided that:

1) X-R_1 is other than hydrogen or methyl;
2) when R_9 and R_{10} are substituents on the A-ring, they are other than mono- or di-methoxy;
3) when R_2 and R_3 are taken together to form =CHR_{11} or =O wherein R_{11} is -O(C_1-C_6)alkyl, then X-R_1 is other than (C_1-C_4)alkyl;
4) when R_2 and R_3 taken together are C=O and R_9 is hydrogen on the A-ring; or when R_2 is hydroxy, R_3 is hydrogen and R_9 is hydrogen on the A-ring, then R_{10} is other than -O-(C_1-C_6)alkyl or -O-CH_2-phenyl at the 2-position of the A-ring;
5) when X-R_1 is (C_1-C_4)alkyl, (C_2-C_4)alkenyl or (C_2-C_4)alkynyl, R_9 and R_{10} are other than mono-hydroxy or =O, including the diol form thereof, when taken together; and
6) when X is absent, R_1 is other than a moiety containing a heteroatom independently selected from N, O or S directly attached to the juncture of the B-ring and the C-ring.

[0041] The compounds of formula IA as described above, their pharmaceutically acceptable salts, and methods of preparing such compounds and salts are disclosed in commonly assigned International patent application PCT/

IB00/00366, filed 27 March 2000. This application, referred to above, is incorporated herein by reference in its entirety.

[0042] Specific GR antagonists useful in the practice of the present invention include, without limitation, the following compounds:

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-(4-pyridinylmethyl)-, [4bS-(4bα,7α,8aβ)]-;
2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-(2-pyridinylmethyl)-, [4bS-(4bα,7α,8aβ)]-;
2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-(3-pyridinylmethyl)-, [4bS-(4bα,7α,8aβ)]-;
carbamic acid, [2-(dimethylamino)ethyl]-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl ester,[4bS-(4bα,7α,8aβ)]-;
2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-pyrazinyl-, [4bS-(4bα,7α,8aβ)]-;
2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-(4-pyridinylmethoxy)-, [2R-(2α,4aα,10aβ)];
2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-(2-pyridinylmethoxy)-, [2R-(2α,4aα,10aβ)];
2-phenanthrenecarbonitrile, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-, [4bS-4bα,7α,8aβ)]-;
2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-(1-propynyl)-, [4bS-(4bα,7α,8aβ)]-;
2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-propyl-, [4bS-(4bα,7α,8aβ)]-;
2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-N-(2-pyridinylmethyl)-, [4bS-(4bα,7α,8aβ)]-;
2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(3-pyridinylmethoxy)-2-(3,3,3-trifluoropropyl)-, [2S-(2α,4aα,10aβ)]-;
2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-3-pyridinyl)methoxy]-4a-(phenylmethyl)-2-(3,3,3-trifluoropropyl)-,[2S-(2α,4aα,10aβ)]-;
2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-(3,3,3-trifluoropropyl)-, (4bS,7S,8aR);
2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-methyl-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-, (4bS,7R,8aR)-;
2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-methyl-4b-(phenylmethyl)-N-3-pyridinyl-, (4bS,7R,8aR)-;
2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-3-pyridinyl)methoxy]-4a-(phenylmethyl)-2-(trifluoromethyl)-, (2R,4aS,10aR)-; and
2-phenanthrenecarboxamide, 4b, 5, 6, 7, 8, 8a, 9, 10-octahydro-7-hydroxy-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-(trifluoromethyl)-, (4bS, 7R, 8aR)-.

[0043] Methods for making the GR antagonists described above are available in the art and disclosed in the above listed patents, applications and published patent applications incorporated by reference herein.

[0044] Acid addition salts of the CRF antagonists and GR antagonists employed in the present invention can be prepared in a conventional manner by treating a solution or suspension of the corresponding free base with one chemical equivalent of a pharmaceutically acceptable acid. Conventional concentration or crystallization techniques can be employed to isolate the salts. Illustrative of suitable acids are acetic, lactic, succinic, maleic, tartaric, citric, gluconic, ascorbic, benzoic, cinnamic, fumaric, sulfuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, sulfamic, sulfonic acids such as methanesulfonic, benzene sulfonic, p-toluenesulfonic, and related acids.

[0045] The administration of the CRF antagonist and the GR antagonist, or pharmaceutically acceptable salts thereof, according to the present invention can be sequential in time or simultaneous, with the simultaneous method being generally preferred. For sequential administration, the CRF antagonist and the GR antagonist can be administered in any order. It is generally preferred that such administration be oral. It is even more preferred that the administration be oral and simultaneous. However, if the subject being treated is unable to swallow, or oral absorption is otherwise impaired or undesirable, another route of administration such as suppositories, parenteral (such as subcutaneous, intravenous, intramuscular, intrasternal and infusion techniques), or topical administration will be appropriate. When the CRF antagonist and the GR antagonist are administered sequentially, the administration of each can be by the same method or by different methods.

[0046] The pharmaceutical compositions of the present invention comprise amounts of a CRF antagonist alone or together with a GR antagonist. One aspect of the present invention provides compositions comprising amounts of a CRF antagonist and a GR antagonist which result in a therapeutic effect. Of such compositions, compositions comprising a CRF antagonist as disclosed in EP 0773023 (which is described above) or a pharmaceutically acceptable salt thereof, and a GR antagonist as disclosed in U.S. Ser. No. 60/132,130 (which is described above) or a pharmaceutically acceptable salt thereof are preferred. It is further preferred that the compositions comprising the CRF antagonist and the GR antagonist be administered in the presence of a pharmaceutically acceptable vehicle, carrier or diluent, in either single or multiple doses.

[0047] Suitable pharmaceutical vehicles, carriers and diluents include inert solid diluents or fillers, sterile aqueous solutions, and various organic solvents. The pharmaceutical compositions formed by combining the active compound (s) and the pharmaceutically acceptable carriers are then readily administered in a variety of dosage forms such as tablets, powders, lozenges, syrups, injectable solutions, and the like. These pharmaceutical compositions can, if desired, contain additional ingredients such as flavorings, binders, excipients, and the like. Thus, for purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate, and calcium phosphate may be employed along with various disintegrants such as starch, alginic acid, and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin, and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate, and talc are often useful for tabletting purposes. Solid compositions of a similar type can also be employed as fillers in soft and hard filled gelatin capsules. Preferred materials for this include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration, the active ingredient(s) therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if desired, emulsifying or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, and combinations thereof.

[0048] For parenteral administration, solutions of the active compound(s) in sesame or peanut oil, aqueous propylene glycol, or in sterile aqueous solution can be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous, and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

[0049] For purposes of transdermal (e.g., topical) administration, dilute, sterile, aqueous or partially aqueous solutions (usually in about 0.1% to 5% concentration), otherwise similar to the above parenteral solutions, are employed.

[0050] Methods of preparing various pharmaceutical compositions with a certain amount of active ingredient(s) are known, or will be apparent in light of this disclosure, to those skilled in the art. For example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 19th Edition (1995).

[0051] A therapeutically effective amount of an active ingredient means an amount that ameliorates, attenuates, or eliminates one or more symptoms of a particular disease or condition or prevents or delays the onset of one of more symptoms of a particular disease or condition. Amount(s) of the CRF antagonist alone or in combination with the GR antagonist necessary to achieve the desired therapeutic effect according to the present invention are within the skill of those who practice in the art of having the benefit of the disclosure herein. Syndrome X-treating or preventing amount (s) of the CRF antagonist alone or in combination with the GR antagonist are preferred.

[0052] In general, the effective dosage for the CRF antagonist employed in the present invention will depend on the intended route of administration and factors such as the age and weight of the patient, as generally known to a physician. The dosage will also depend on the particular condition to be treated and will generally range from about 0.1 to about 300 mg/kg body weight of the patient per day, with administration carried out in single or divided dosages.

[0053] In general, the effective dosage for the GR antagonist employed in the present invention will range from about 0.1 μg/kg of body weight to about 500 mg/kg of body weight, more particularly from about 1 μg/kg to about 250 mg/kg, and most particularly from about 2 μg/kg to about 100 mg/kg. More preferably, the GR antagonist will be administered at an amount of about 0.1 mg/kg to about 500 mg/kg of body weight, and most preferably from about 0.1 mg/kg to about 50 mg/kg of body weight. As recognized by those skilled in the art, the particular quantity of the GR antagonist to be administered to a patient according to the present invention will depend upon a number of factors, including, without limitation, the biological activity desired, the condition of the patient, and tolerance for the drug.

[0054] The methods and compositions of the present invention have utility in the treatment or prevention of Syndrome X in animals, such as dogs, cats, cows, horses, sheep, and humans. Particularly preferred animals are mammals, including both males and females. As such, the methods and compositions of the present invention have utility in the treatment or prevention of Syndrome X in companion animals, such as dogs and cats. The administration of the compositions of this invention may be effected orally or parenterally. An amount of a composition of the invention is administered such that an effective dose is received, usually a daily dose.

[0055] Conveniently, the medicaments can be carried in the drinking water such that a therapeutic dosage of the agent(s) is ingested with the daily water supply. The agent(s) can be directly metered into drinking water, preferably in the form of a liquid, water-soluble concentrate, such as an aqueous solution of a water-soluble salt. Conveniently,

the active ingredient(s) can also be added directly to the companion animal's feed, as such, or in the form of an animal feed supplement, also referred to as a premix or concentrate. A premix or concentrate of the therapeutic agent(s) in a carrier is more commonly employed for the inclusion of the agent in the feed. Suitable carriers are liquid or solid, as desired, such as water, various meals such as alfalfa meal, soybean meal, cottonseed oil meal, linseed oil meal, corncob meal and corn meal, molasses, urea, bone meal, and various mineral mixes. A particularly effective carrier is the respective animal feed itself, i.e., a small portion of such feed. The carrier facilitates uniform distribution of the active material(s) in the finished feed with which the premix is blended. It is important that the compound(s) be thoroughly blended into the premix and, subsequently, the feed. In this respect, the agent(s) may be dispersed or dissolved in a suitable oily vehicle such as soybean oil, corn oil, cottonseed oil, and the like, or in a volatile organic solvent and then blended with the carrier. It will be appreciated that the proportions of active material(s) in the concentrate are capable of wide variation since the amount of agent(s) in the finished feed may be adjusted by blending the appropriate proportion of premix with the feed to obtain a desired level of the therapeutic agent(s).

[0056] High potency concentrates may be blended by the feed manufacturer with a proteinaceous carrier such as soybean oil meal and other meals, as described above, to produce concentrated supplements which are suitable for direct feeding to animals. In such instances, the animals are permitted to consume the usual diet. Alternatively, such concentrated supplements may be added directly to the feed to produce a nutritionally balanced, finished feed containing a therapeutically effective amount of the compound(s) according to the present invention. The mixtures are thoroughly blended by standard procedures, such as in a twin shell blender, to insure homogeneity.

[0057] If the supplement is used as a top dressing for the feed, it likewise helps to insure uniformity of distribution of the active ingredient(s) across the top of the dressed feed.

[0058] For veterinary uses, both paste and pellet formulations may also be conveniently employed. Paste formulations can be prepared readily by dispersing the active compound(s) in a pharmaceutically acceptable oil such as peanut oil, sesame oil, corn oil, and the like. Similarly, pellets containing an effective amount of the compound(s) of the present invention can be prepared by admixing the compound(s) of the invention with a suitable diluent such as carbowax, carnuba wax, and the like, and a lubricant, such as magnesium or calcium stearate, can be employed to improve the pelleting process.

[0059] Since one aspect of the present invention relates to the treatment or prevention of Syndrome X with a combination of active ingredients which may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. A kit, according to this invention, comprises two separate pharmaceutical compositions: a first unit dosage form, comprising a therapeutically effective amount of a CRF antagonist and a pharmaceutically acceptable vehicle, carrier or diluent, and a second unit dosage form comprising a therapeutically effective amount of a GR antagonist and a pharmaceutically acceptable vehicle, carrier or diluent. The kit further comprises a container. The container is used to contain the separate compositions and may comprise, for example, a divided bottle or a divided foil packet; however, the separate compositions may also be contained within a single, undivided container. Normally, the kit will also include directions for the administration of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage levels, or when titration of the individual components of the combination is desired by the prescribing physician.

[0060] An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being used widely for the packaging of pharmaceutical unit dosage forms (tablets, capsules and the like). Blister packs generally consist of a sheet of relatively rigid material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The recesses generally conform to the size and shape of the tablets or capsules to be contained therein. Next, the tablets or capsules are placed in the recesses and the sheet of relatively rigid material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. Preferably, the strength of the sheet is such that the tablets or capsules may be removed from the blister pack by the application of manual pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed through the formed opening.

[0061] It is further desirable to provide a memory aid on the pack, e.g., in the form of numbers or similar indicia next to the tablets or capsules whereby the indicia correspond with the days of the regimen which the dosage form so specified is to be ingested. An additional example of such a memory aid is a calendar printed on the pack, e.g., as follows "First Week, Monday, Tuesday, ... etc.... Second Week, Monday, Tuesday, ... " etc. Other variations will be readily apparent. A "daily dose" can be a single tablet or capsule or multiple tablets or capsules to be ingested on a given day. Also, a daily dose of a CRF antagonist can consist of one tablet or capsule while a daily dose of a GR antagonist can consist of multiple tablets or capsules, or vice versa. The memory aid should reflect this.

[0062] In another specific embodiment of the invention, a pack designed to dispense the daily doses one at a time in the order of their intended use is provided. Preferably, the pack is equipped with a memory aid, so as to further facilitate compliance with the dosage regimen. An example of such a memory aid is a mechanical counter which indi-

cates the number of daily doses to be dispensed. Another example of such a memory aid is a battery-powered microchip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds the patient when the next dose is to be taken.

[0063] The following references disclose animal models, such as the JCR:LA-corpulent (cp) rat or the obese Zucker rat, that may be used to determine the Syndrome X-treating activity of the compound(s) employed to practice the present invention: J.C. Russell et al., Metabolism, Vol. 48, No. 6 (June), 1999: pp 701-706; Diabetes 46:1958-1964, 1997.

[0064] Methods that may be used to determine CRF antagonist activity of the compounds employed to practice the present invention are as described in, e.g., Wynn et al., Endocrinology, 116:1653-1659 (1985), and Grigoriadis et al., Peptides, 10:179-188 (1989). Methods that can be used to determine the CRF binding protein inhibiting activity of compounds employed to practice the present invention are described in Brain Research, (1997), 745(1,2), 248-256. These methods determine the binding affinity of a test compound for a CRF receptor, which is highly related to its expected activity as a CRF antagonist.

[0065] Methods that may be used to determine GR antagonist activity of the compounds employed to practice the present invention are described below and in commonly assigned U.S. patent application, Ser. No. 60/132, 130, filed 30 April 1999, which is hereby incorporated by reference herein. These methods determine the binding affinity of a test compound for a GRA receptor, which is highly related to its expected activity as a GR antagonist.

[0066] The following is a description of an assay for the identification of glucocorticoid receptor antagonists/agonists: HeLa cells (American Type Culture Collection (ATCC), Rockville, MD) containing endogenous human glucocorticoid receptors are transfected with a 3x pLuxF47-GRE-luciferase plasmid generated by standard procedures and a plasmid conferring neomycin resistance. pLuxF47-GRE was constructed by annealing oligonucleotides 23907-26A and 23907-26B and ligating into the Bg I II and Eag I sites of pLuxF47. Novel glucocorticoid responsive cell lines are generated and characterized. One such cell line designated HeLa-GRE9 is used for determining the activity of compounds at the glucocorticoid receptor. Cells are maintained in charcoal-stripped serum and transferred to 96-well microtiter plates one day prior to treatment with various concentrations (10^{-12} to 10^{-5}) of test compounds in the absence and presence of known glucocorticoid receptor agonists (i.e., dexamethasone, hydrocortisone) for up to 24 hours. Treatments are performed in triplicate. Cell lysates are prepared and luciferase activity is determined using a luminometer. Agonist activity is assessed by comparing the luciferase activity from cells treated with test compound to cells treated with the agonist dexamethasone. Antagonist activity is assessed by comparing the luciferase activity of an EC_{50} concentration of dexamethasone in the absence and presence of test compound. The EC_{50} (concentration that produced 50% of the maximal response) for dexamethasone is calculated from dose response curves.

[0067] The following is a description of an assay for determining the competitive inhibition binding of the Human Type II Glucocorticoid receptor expressed in Sf9 cells:

[0068] Binding protocol: Compounds are tested in a binding displacement assay using human glucocorticoid receptor expressed in Sf9 cells with ^{3}H-dexamethasone as the ligand. Human glucorticoid receptor is expressed in Sf9 cells as described in Mol. Endocrinology 4: 209, 1990. Pellets containing Sf9 cells expressing the human GR receptor from 1L vats are lysed with 40 ul of 20mM AEBSF stock (Calbiochem, LaJolla, CA) containing 50 mg/ml leupeptin and 40 ml of homogenization buffer is added. The assay is carried out in 96-well polypropylene plates in a final volume of 130 ul containing 200 ug Sf9 lysate protein, 6.9 nM ^{3}H-dexamethasone (Amersham, Arlington Heights, IL) in presence of test compounds, test compound vehicle (for total counts) or excess dexamethasone (7 uM non-radioactive, to determine non-specific binding) in an appropriate volume of assay buffer. All compounds are tested at 6 concentrations in duplicate (concentration range 0.1-30 nM or 3-1000 nM). Test compounds are diluted from a 25 mM stock in 100% DMSO with 70%EtOH and added in a volume of 2 µl. Once all additions are made the plates are shaken, sealed with sealing tape and incubated at 4 °C overnight.

[0069] After the overnight incubation, unbound counts are removed with dextran coated charcoal as follows: 75 µl of dextran coated charcoal (5.0 g activated charcoal, 0.5 g dextran adjusted to volume of 100 ml with assay buffer) is added, plates are shaken and incubated for five minutes at 4 °C. Plates are then centrifuged in a refrigerated benchtop centrifuge at top speed for 15 minutes. 100 µl of the supernatant from each well is placed into a 96-well PET plate with 200 µl of scintillation cocktail and counted on a beta counter (1450 MicroBetaTrilux, from Wallac, Turku, Finland).

[0070] Data analysis: After subtracting non-specific binding, counts bound are expressed as % of total counts. The concentration response for test compounds are fitted to a sigmoidal curve to determine the IC_{50} (concentration of compound that displaces 50% of the bound counts).

[0071] Reagents: Assay Buffer: 2.0 ml 1M Tris (pH 7.4), 0.2 ml 0.5mM EDTA (pH 8.0), 77.1 mg DTT, 0.243 g sodium molybdate in a volume of 100 ml water; Homogenization buffer: 2.0 ml 0.5 M K_2HPO_4 (pH 7.6), 20 µl 0.5 M EDTA (pH 8.0), 77.1 mg DTT, 0.486 g sodium molybdate in a volume of 100 ml water.

[0072] The following is a description of an assay for determining receptor selectivity: T47D cells (American Type Culture Collection (ATCC), Rockville, MD) containing endogenous human progesterone and mineralocorticoid receptors are transiently transfected with a 3x pLuxF47-GRE-luciferase using Lipofectamine Plus (GIBCO-DRL, Gaithers-

burg, MD). Twenty-four hours post-transfection cells are maintained in charcoal-stripped serum and transferred to 96-well microtiter plates. The next day cells are treated with various concentrations (10^{-12} to 10^{-5}) of test compounds in the absence and presence of a known progesterone receptor agonist (progesterone) and a known mineralocorticoid receptor agonist (aldosterone) for up to 24 hours. Treatments are performed in triplicate. Cell lysates are prepared and luciferase activity is determined using a luminometer. Agonist activity is assessed by comparing the luciferase activity from cells treated with compound alone to cells treated with either the agonist progesterone or aldosterone. Antagonist activity is assessed by comparing the luciferase activity of an EC_{50} concentration of progesterone or aldosterone in the absence and presence of compound. The EC_{50} (concentration that produced 50% of maximal response) for progesterone and aldosterone is calculated from dose response curves.

[0073] The following is a description of an assay for determining anti-diabetes and anti-obesity activity. The obese, diabetic ob/ob mouse is used to assess the anti-diabetes and anti-obesity activity of the compounds. Six to 10 week old ob/ob male mice (Jackson Labs, Bar Harbor, Maine) are dosed with test compound(s) for 2 to 10 days. Plasma glucose levels are determined by measuring glucose from samples obtained by orbital bleeding. Glucose is quantitated using an Abbott Autoanalyzer (Abbott, Inc., Abbott Park, IL). Food intake is monitored on a daily basis by differential weighing.

[0074] The following is a description of an assay for determining the ability of a compound to inhibit glucocorticoid agonist induction of liver tyrosine amino transferase (TAT) activity in conscious rats:

[0075] Animals: Male Sprague Dawley rats (from Charles River, Willimington MA) (adrenal-intact or adrenalectomized at least one week prior to the screen) b.w. 90g are used. The rats are housed under standard conditions for 7-10d prior to use in the screen.

[0076] Experimental protocol: Rats (usually 3 per treatment group) are dosed with test compound, vehicle or positive control (RU486) either i.p., p.o., s.c.or i.v. (tail vein). The dosing vehicle for the test compounds is typically one of the following: 100% PEG 400, 0.25% methyl cellulose in water, 70% ethanol or 0.1 N HCl and the compounds are tested at doses ranging from 10 to 125 mg/kg. The compounds are dosed in a volume of 1.0 ml/ 100 g body weight (for p.o.) or 0.1 ml/100g body weight for other routes of administration . Ten minutes after the administration of the test compound, the rats are injected with dexamethasone (0.03 mg/kg i.p. in a volume of 0.1 ml/ 100g) or vehicle. To prepare the dexamethasone dosing solution, dexamethasone (from Sigma, St. Louis, MO) is dissolved in 100% ethanol and diluted with water (final: 10% ethanol:90% water, vol:vol). Groups treated with vehicle-vehicle, vehicle-dexamethasone, and Ru486-dexamethasone are included in each screen. The compounds are tested vs. dexamethasone only. Three hours after the injection of dexamethasone the rats are sacrificed by decapitation. A sample of liver (0.3 g) is excised and placed in 2.7 ml of ice cold buffer and homogenized with a polytron. To obtain cytosol the liver homogenate is centrifuged at 105,000g for 60 min and the supernatant is stored at -80 °C until analysis. TAT is assayed on 100 ul of a 1:20 dilution of the 105,000g supernatant using the methods of D.K. Granner and G.M. Tomkins, "Tyrosine Aminotransferase (Rat Liver)," Methods in Enzymology, 17A: 633-637 (1970)) and a reaction time of 8-10 minutes. TAT activity is expressed as umol product/min/g liver.

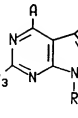
[0077] Interpretation: Treatment data are analyzed by using analysis of variance (ANOVA) with protected least significant difference (PLSD) post-hoc analysis. Compounds are considered active in this test if the TAT activity in the group pretreated with compound prior to dexamethasone administration is significantly ($P < 0.05$) decreased relative to the TAT activity in the vehicle-dexamethasone treated group.

Claims

1. Use of a corticotropin releasing factor antagonist for the manufacture of a medicament for treating or preventing Syndrome X in an animal which comprises administering to said animal an amount of a corticotropin releasing factor antagonist.

2. The use of claim 1 wherein a therapeutically effective amount of a corticotropin releasing factor antagonist is administered.

3. The use of claim 2 wherein the corticotropin releasing factor antagonist is a compound of formula



and the pharmaceutically acceptable acid addition salts thereof, wherein

A is NR_1R_2, $CR_1R_2R_{11}$, or $C(=CR_1R_{12})R_2$, $NHCR_1R_2R_{11}$, $OCR_1R_2R_{11}$, $SCR_1R_2R_{11}$, $NHNR_1R_2$, $CR_2R_{11}NHR_1$, $CR_2R_{11}OR_1$, $CR_2R_{11}SR_1$ or $C(O)R_2$;

R_1 is hydrogen, or C_1-C_6 alkyl which may be substituted by one or two substituents R_6 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, O-C(O)-(C_1-C_6 alkyl), O-C(O)-N(C_1-C_4 alkyl)(C_1-C_2 alkyl); amino, NH(C_1-C_4 alkyl), S(C_1-C_6 alkyl), OC(O)NH(C_1-C_4 alkyl), N(C_1-C_2 alkyl)C(O)(C_1-C_4 alkyl), NHC(O)(C_1-C_4 alkyl), COOH, CO(C_1-C_4 alkyl), C(O)NH(C_1-C_4 alky), C(O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, CN, NO_2, SO(C_1-C_4 alkyl); SO_2(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), and said C_1-C_6 alkyl may have one or two double or triple bonds;

R_2 is C_1-C_{12} alkyl, aryl or (C_1-C_{10} alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, oxazolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or (C_1-C_6 alkylene) cycloalkyl, wherein said cycloalkyl may have one or two of O, S or N-Z, wherein Z is hydrogen, substituted , independently, for one or two carbons of said cycloalkyl, C_1-C_4 alkyl, benzyl or C_1-C_4 alkanoyl, wherein R^2 may be substituted independently by from one to three of chloro, fluoro, or C_1-C_4 alkyl, or one of hydroxy, bromo, iodo, C_1-C_6 alkoxy, OC(O)(C_1-C_6 alkyl), O-C-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), S(C_1-C_6 alkyl), NH_2, NH(C_1-C_4 alkyl), N(C_1-C_4 alkyl) C(O)(C_1-C_4 alkyl), NHC(O)(C_1-C_4 alkyl), COOH, C(O)O(C_1-C_4 alkyl), C(O)NH(C_1-C_4 alkyl), C(O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, CN, NO_2, SO(C_1-C_4 alkyl), SO_2(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), and wherein said C_1-C_{12} alkyl or C_1-C_{10} alkylene may have one to three double or triple bonds; or

NR_1R_2 or $CR_1R_2R_{11}$ may form a 4- to 8-membered ring optionally having one or two double bonds or one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, benzyl, or C_1-C_4 alkanoyl;

R_3 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, O(C_1-C_6 alkyl), NH(C_1-C_6 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, S(C_1-C_4 alkyl), SO(C_1-C_4 alkyl), or SO_2(C_1-C_4 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may have one or two double or triple bonds and may be substituted by from 1 to 3 R_7 substituents independently selected from the group consisting of hydroxy, amino, C_1-C_3 alkoxy, dimethylamino, diethylamino, methylamino, ethylamino, NHC(O)CH_3, fluoro, chloro or C_1-C_3 thioalkyl;

R_4 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, amino, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_2 alkyl), SO_n(C_1-C_6 alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, carboxy, or amido, wherein said C_1-C_6 alkyls may be substituted by one to three of hydroxy, amino, carboxy, amido, NHC(O)(C_1-C_4 alkyl), NH(C_1-C_4 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl), C(O)O(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, piperazinyl, piperidinyl, or tetrazolyl, wherein each one of the above groups may be substituted independently by from one to three of fluoro, chloro, bromo, formyl, C_1-C_6 alkyl, C_1-C_6 alkoxy or trifluoromethyl, or one of hydroxy, iodo, cyano, nitro, amino, cyclopropyl, NH(C_1-C_4 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl), COO(C_1-C_4 alkyl), CO(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SO_2NH_2, $NHSO_2$(C_1-C_4 alkyl), S(C_1-C_6 alkyl), SO_2(C_1-C_6 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may have one double or triple bond and may be substituted by one or two of fluoro, chloro, hydroxy, amino, methylamino, dimethylamino or acetyl; with the proviso that R_5 is not unsubstituted phenyl;

R_{11} is hydrogen, hydroxy, fluoro, chloro; COO(C_1-C_2 alkyl), cyano, or CO(C_1-C_2 alkyl); and

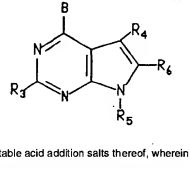
R_{12} is hydrogen or C_1-C_4 alkyl;

(a) A is not straight chain C_1-C_{12} alkyl;

(b) when R_5 is hydrogen, A is benzyl or phenethyl, and R_4 is fluoro, chloro, bromo or iodo, then R_5 is not 5'-deoxy-ribofuranosyl or 5'-amino-5'-deoxyribofuranosyl; and

(c) when R^5 is phenyl, said phenyl is substituted by two or three substituents.

4. The use of claim 2 wherein the corticotropin releasing factor antagonist is a compound of formula



and the pharmaceutically acceptable acid addition salts thereof, wherein

B is NR_1R_2, $CR_1R_2R_{11}$, $C(=CR_2R_{12})R_1$, $NHR_1R_2R_{11}$, $OCR_1R_2R_{11}$, $SCR_1R_2R_{11}$, $NHNR_1R_2$, $CR_2R_{11}NHR_1$, $CR_2R_{11}OR_1$, $CR_2R_{11}SR_1$, or $C(O)R_2$;

R_1 is hydrogen, or C_1-C_6 alkyl which may be substituted by one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, C_1-C_8 alkoxy, O-C(=O)-(C_1-C_6 alkyl), O-C(=O)NH(C_1-C_4 alkyl), O-C(=O)-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), amino, NH(C_1-C_4 alkyl), N(C_1-C_2 alkyl)(C_1-C_4 alkyl), S(C_1-C_6 alkyl), N(C_1-C_4alkyl)C(=O)(C_1-C_4 alkyl), NH(C_1-C_4 alkyl), COOH, C(=O)O(C_1-C_4 alkyl), C(=O)NH(C_1-C_4 alkyl), C(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, CN, NO_2, SO(C_1-C_4 alkyl), SO_2(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), and said C_1-C_6 alkyl may contain one or two double or triple bonds;

R_2 is C_1-C_{12} alkyl, aryl or (C_1-C_{10} alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benziso-thiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopy-ridyl, oxazolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or (C_1-C_6 alkylene) cycloalkyl, wherein said cy-cloalkyl may contain one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, benzyl or C_1-C_4 alkanoyl, wherein R_2 may be substituted independently by from one to three of chloro, fluoro, or C_1-C_4 alkyl, or one of hydroxy, bromo, iodo, C_1-C_6 alkoxy, O-C(=O)-(C_1-C_6 alkyl), O-C-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), S(C_1-C_6 alkyl), NH_2, NH(C_1-C_2 alkyl), N(C_1-C_2 alkyl) (C_1-C_4 alkyl), N(C_1-C_4)- C(=O)(C_1-C_4 alkyl), NHC(=O)(C_1-C_4), COOH, C(=O)O(C_1-C_4 alkyl), C(=O)NH(C_1-C_4 alkyl), C(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, CN, NO_2, SO(C_1-C_4 alkyl), SO_2(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), and wherein said C_1-C_{12} alkyl or C_1-C_{10} alkylene may contain one to three double or triple bonds; or

NR_1R_2 or $CR_1R_2R_{11}$ may form a saturated 3- to 8 membered carbocyclic ring of which the 5- to 8-membered ring contain one or two double bonds or one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, benzyl or C_1-C_4 alkanoyl;

R_3 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, O(C_1-C_6 alkyl), NH(C_1-C_6 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, S(C_1-C_4 alkyl), SO(C_1-C_4 alkyl), or SO_2(C_1-C_4 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may contain from one or two double or triple bonds and may be substituted by from 1 to 3 substituents R_5 independently selected from the group consisting of hydroxy, amino, C_1-C_3 alkoxy, dimethyl-amino, diethylamino, methylamino, ethylamino, $NHCH_3$, fluoro, chloro or C_1-C_3 thioalkyl;

R_4 and R_6 are each independently hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, amino, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_2 alkyl), SO_n(C_1-C_6 alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, carboxy, or amido, wherein said C_1-C_8 alkyls may be substituted by one to three of hydroxy, amino, carboxy, amido, NHC(=O)(C_1-C_4 alkyl), NH(C_1-C_4 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl), C(=O)O(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

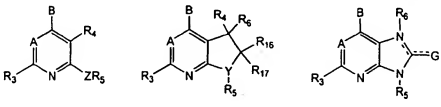
R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzo-furanyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, tri-azolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, piperidinyl, piperazinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, optionally containing one to three of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl or phenyl-methyl, wherein each one of the above groups may be substituted independently by from one to four of fluoro, chloro, C_1-C_6 alkyl, C_1-C_6 alkoxy or trifluoromethyl, or one of bromo, iodo, cyano, nitro, amino, NH(C_1-C_4 alkyl), N(C_1-C_4)(C_1-C_2 alkyl), COO(C_1-C_4 alkyl), CO(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C, alkyl)(C_1-

C_2 alkyl), SO_2NH_2, $NHSO_2(C_1$-C_4 alkyl), $S(C_1$-C_6 alkyl), $SO_2(C_1$-C_6 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may be substituted by one or two of fluoro, chloro, hydroxy, amino, methylamino, dimethylamino or acetyl; with the proviso that R_5 is not unsubstituted phenyl;

R_{11} is hydrogen, hydroxy, fluoro, chloro, $COO(C_1$-C_2 alkyl), cyano, or $CO(C_1$-C_2 alkyl); and

R_{12} is hydrogen or C_1-C_4 alkyl; with the proviso that (1) when R_5 is 4-bromophenyl, R_3 is hydrogen, and R_4 and R_6 are methyl, then B is not methylamino or ethyl, and (2) when R_5 is 4-bromophenyl, and R_3, R_4 and R_6 are methyl, then B is not 2-hydroxyethylamino.

5. The use of claim 2 wherein the corticotropin releasing factor antagonist is a compound of formula



wherein

A is CR_7 or N;

B is NR_1R_2, $CR_1R_2R_{11}$, $C(=CR_2R_{12})R_1$, $NHCHR_1R_2$, $OCHR_1R_2$, $SCHR_1R_2$, CHR_2OR_{12}, CHR_2SR_{12}, $C(S)R_2$ or $C(O)R_2$;

G is oxygen, sulfur, NH, NH_2, hydrogen, methoxy, ethoxy, trifluoromethoxy, methyl, ethyl, thiomethoxy, NH_2, $NHCH_3$, $N(CH_3)_2$ or trifluromethyl;

Y is CH or N;

Z is NH, O, S, N (C_1-C_2 alkyl), or $CR_{13}R_{14}$, wherein R_{13} and R_{14} are each independently hydrogen, trifluoromethyl, or C_1-C_4 alkyl, or one of R_{13} and R_{14} may be cyano, chloro, bromo, iodo, fluoro, hydroxy, $O(C_1$-C_2 alkyl), amino, $NH(C_1$-C_2 alkyl), or $CR_{13}R_{14}$ may be C=O or cydopropyl;

R_1 is C_1-C_8 alkyl which may be substituted by one or two substituents R_8 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, O-CO-(C_1-C_4 alkyl), O-CO-NH(C_1-C_4 alkyl), O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), NH(C_1-C_4 alkyl), N(C_1-C_2 alkyl)(C_1-C_4 alkyl), S(C_1-C_4 alkyl), N(C_1-C_4alkyl)CO(C_1-C_4 alkyl), NHCO(C_1-C_4 alkyl), COO(C_1-C_4 alkyl), CONH(C_1-C_4 alkyl), CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), S(C_1-C_4 alkyl), CN, NO_2, SO(C_1-C_4 alkyl), SO_2(C_1-C_4 alkyl), and said C_1-C_8 alkyl or C_1-C_4 alkyl may contain one double or triple bond;

R_2 is C_1-C_{12} alkyl, aryl or (C_1-C_4 alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or (C_1-C_6 alkylene)cycloalkyl, wherein said cycloalkyl may contain one or two of O, S or N-R_9 wherein R_9 is hydrogen, or C_1-C_4 alkyl, wherein the above defined R_2 may be substituted independently by from one to three of chloro, fluoro, or C_1-C_4 alkyl, or one of bromo, iodo, C_1-C_6 alkoxy, O-CO-(C_1-C_6 alkyl), O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), S(C_1-C_6 alkyl), CN, NO_2, SO(C_1-C_4 alkyl), or SO_2(C_1-C_4 alkyl), and wherein said C_1-C_{12} alkyl or C_1-C_4 alkylene may contain one double or triple bond; or

NR_1R_2 or $CR_1R_2R_{11}$ may form a saturated 5- to 8-membered carbocyclic ring which may contain one or two double bonds or one or two of O or S;

R_3 is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF_3, methylthio, methylsulfonyl, CH_2OH or CH_2OCH_3;

R_4 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, amino, nitro, $NH(C_1$-C_4 alkyl), $N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), $SO_n(C_1$-C_4 alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, CO(C_1-C_4 alkyl), CHO, or COO(C_1-C_4 alkyl), wherein said C_1-C, alkyl may contain one or two double or triple bonds and may be substituted by one or two of hydroxy, amino, carboxy, $NHCOCH_3$, $NH(C_1$-C_2 alkyl), $N(C_1$-C_2 alkyl)$_2$, $COO(C_1$-C_4 alkyl), $CO(C_1$-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, chloro, cyano or nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, furanyl, benzofuranyl, benzothiazolyl, or indolyl, wherein each one of the above groups R_5 is substituted independently by from one to three of fluoro, chloro, C_1-C_6 alkyl, or C_1-C_6 alkoxy, or one of hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, $NH(C_1$-C_4 alkyl), $N(C_1$-$C_6)(C_1$-C_2 alkyl), COOH, $COO(C_1$-C_4 alkyl), $CO(C_1$-C_4 alkyl),

$SO_2NH(C_1$-C_4 alkyl), $SO_2N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), SO_2NH_2, $NHSO_2(C_1$-C_4 alkyl), $S(C_1$-C_6 alkyl), or SO_2 (C_1-C_6 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may be substituted by one or two of fluoro, hydroxy, amino, methylamino, dimethylamino or acetyl;

R_6 is hydrogen, or C_1-C_6 alkyl, wherein said C_1-C_6 alkyl may be substituted by one hydroxy, methoxy, ethoxy or fluoro;

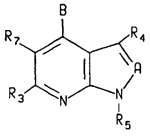
R_7 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, $O(C_1$-C_4 alkyl), $C(O)(C_1$-C_4 alkyl), or $C(O)O(C_1$-C_4 alkyl), wherein the C_1-C_4 alkyl groups may be substituted with one hydroxy, chloro or bromo, or one to three fluoro;

R_{11} is hydrogen, hydroxy, fluoro, or methoxy;

R_{12} is hydrogen or C_1-C_4 alkyl; and

R_{16} and R_{17} are each independently hydrogen, hydroxy, methyl, ethyl, methoxy, or ethoxy, except that they are not both methoxy or ethoxy, and CR_4R_6 and $CR_{16}R_{17}$ each independently may be C=O.

6. The use of claim 2 wherein the corticotropin releasing factor antagonist is a compound of formula



and the pharmaceutically acceptable acid addition salts thereof, wherein

A is N or $-CR_6$;

B is $-NR_1R_2$, $-CR_1R_2R_{11}$, $-C(=CR_2R_{12})R_1$, $-NHCHR_1R_2$, $-OCHR_1R_2$, $-SCHR_1R_2$, $-CHR_2OR_{12}$, $-CHR_2SR_{12}$, $-C(S)R_1$ or $-C(O)R_1$;

R_1 is C_1-C_6 alkyl which may optionally be substituted with one or two substituents independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, $-O$-CO-(C_1-C_4 alkyl), $-O$-CO-NH(C_1-C_4 alkyl), $-O$-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), $-NH$(C_1-C_4 alkyl), $-N$(C_1-C_2 alkyl)(C_1-C_4 alkyl), $-S$(C_1-C_4 alkyl), $-N$(C_1-C_4alkyl)CO(C_1-C_4 alkyl), $-NHCO$(C_1-C_4 alkyl), $-COO$(C_1-C_4 alkyl), $-CONH$(C_1-C_4 alkyl), $-CON$(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, $-SO$(C_1-C_4 alkyl), $-SO_2$(C_1-C_4 alkyl), and wherein any of the foregoing C_1-C_4 alkyl and C_1-C_6 alkyl groups may optionally contain one carbon-carbon double or triple bond;

R_2 is C_1-C_{12} alkyl, aryl, $-$(C_1-C_4 alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, oxazolyl, or benzoxazolyl; or 3- to 8-membered cycloalkyl or $-$(C_1-C_6 alkylene)cycloalkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said $-$(C_1-C_6 alkylene)cycloalkyl having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom or by N-Z wherein Z is hydrogen; or C_1-C_4 alkyl, and wherein each of said groups R_2 may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, and C_1-C_4 alkyl, or by one substituent selected from bromo, iodo, C_1-C_6 alkoxy, $-O$-CO-(C_1-C_6 alkyl), $-S$(C_1-C_6 alkyl), $-COO$(C_1-C_4 alkyl), CN, NO_2, $-SO$(C_1-C_4 alkyl), and $-SO_2$(C_1-C_4 alkyl), and wherein said C_1-C_{12} alkyl and the C_1-C_4 alkylene moiety of said $-$(C_1-C_4 alkylene)aryl may optionally contain one carbon-carbon double or triple bond;

or $-NR_1R_2$ may form a saturated 5- to 8-membered heterocyclic ring, or $-CHR_1R_2$ may form a saturated 5- to 8-membered carbocyclic ring, wherein each of these rings may optionally contain one or two carbon-carbon double bonds and wherein one or two of the carbon atoms of each of these rings may optionally be replaced with a sulfur or oxygen atom;

R_3 is C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, $-CH_2OH$, $-CH_2OCH_3$, $-O$(C_1-C_3 alkyl), $-S$(C_1-C_3 alkyl), or $-SO_2$(C_1-C_3 alkyl), wherein said C_1-C_3 alkyl may optionally contain one carbon-carbon double or triple bond;

R_4 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, amino, $-NHCH_3$, $-N(CH_3)_2$, $-CH_2OH$, $-CH_2OCH_3$, or $-SO_n$(C_1-C_4 alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, $-CO$(C_1-C_4 alkyl), $-CHO$, or $-COO$(C_1-C_4 alkyl) wherein the C_1-C_4 alkyl moieties in the foregoing R_4 groups may optionally contain one carbon-

carbon double or triple bond;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, pyrimidyl, benzofuranyl, pyrazinyl or benzothiazolyl, wherein each one of said groups R_5 may optionally be substituted with from one to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl and C_1-C_6 alkoxy, or by one substituent selected from iodo, hydroxy, bromo, formyl, cyano, nitro, amino, trifluoromethyl, -NH(C_1-C_4 alkyl), -N(C_1-C_6)(C_1-C_2 alkyl), -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -COOH, -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SO_2NH_2, -$NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and -SO_2(C_1-C_6 alkyl), wherein each of said C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the foregoing R^5 groups may optionally be substituted with one to three fluorine atoms;

R_6 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, -CH_2OH, -CH_2OCH_3, or C_1-C_4 alkoxy;

R_7 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, -O(C_1-C_4 alkyl), cyano, -CH_2OH, -CH_2O(C_1-C_2 alkyl), -CO(C_1-C_2 alkyl), or -COO(C_1-C_2 alkyl);

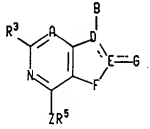
R_{11} is hydrogen, hydroxy, fluoro, or methoxy; and

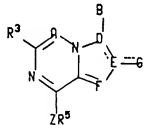
R_{12} is hydrogen or C_1-C_4 alkyl;

with the proviso that when A is N, then: (a) B is not unsubstituted alkyl; (b) R_5 is not unsubstituted phenyl or monosubstituted phenyl; and (c) R_3 is not unsubstituted alkyl;

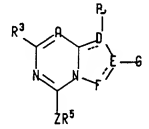
or a pharmaceutically acceptable salt of such compound.

7. The use of claim 2 wherein the corticotropin releasing factor antagonist is a compound of formula





or



or a pharmaceutically acceptable salt thereof, wherein

the dashed lines represent optional double bonds;

A is nitrogen or CR^7;

B is -NR^1R^2, -$CR^1R^2R^{10}$, -C(=CR^2R^{11})R^1, -$NHCR^1R^2R^{10}$, -$OCR^1R^2R^{10}$, -$SCR^1R^2R^{10}$, -$CR^2R^{10}NHR^1$, -$CR^2R^{10}OR^1$, -$CR^2R^{10}SR^1$ or -COR^2;

D is nitrogen and is single bonded to all atoms to which it is attached, or D is carbon and is either double bonded to E in formulas I and II or double bonded to the adjacent carbon atom common to both fused rings in formula III, or D is CH and is single bonded to E in formulas I and II;

E is nitrogen, CH or carbon;

F is oxygen, sulfur, CHR^4 or NR^4 when it is single bonded to E and F is nitrogen or CR^4 when it is double bonded to E;

G, when single bonded to E, is hydrogen, C_1-C_4 alkyl, -S(C_1-C_4 alkyl), -O(C_1-C_4 alkyl), NH_2, -NH(C_1-C_4 alkyl) or -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), wherein each of the C_1-C_4 alkyl groups of G may optionally be substituted with

one hydroxy, -O(C_1-C_2 alkyl) or fluoro group; G, when double bonded to E, is oxygen, sulfur or NH; and G, when E is nitrogen and double bonded to D or F, is absent;

R^1 is hydrogen, C_1-C_6 alkyl optionally substituted with one or two substituents R^8 independently selected from hydroxy, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, CF_3, -C(=O)O-(C_1-C_4)alkyl, -OC(=O)(C_1-C_4 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -CN, $-NO_2$, -SO(C_1-C_4 alkyl), $-SO_2$(C_1-C_4 alkyl), $-SO_2NH$(C_1-C_4 alkyl) and $-SO_2N$(C_1-C_4 alkyl)(C_1-C_2 alkyl), wherein each of the C_1-C_4 alkyl groups in the foregoing R^1 groups may optionally contain one or two double or triple bonds;

R^2 is C_1-C_{12} alkyl which may optionally contain from one to three double or triple bonds, aryl or (C_1-C_4 alkylene)aryl, wherein said aryl and the aryl moiety of said (C_1-C_4 alkylene)aryl is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; C_3-C_8 cycloalkyl or (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl), wherein one or two of the carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl) may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^2 wherein Z^2 is selected from hydrogen, C_1-C_4 alkyl, benzyl and C_1-C_4 alkanoyl, and wherein each of the foregoing R^2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, hydroxy and C_1-C_4 alkyl, or with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -OC(=O)(C_1-C_6 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), amino, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)-CO-(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SH, -CN,-NO_2, -SO(C_1-C_4 alkyl), $-SO_2$(C_1-C_4 alkyl), $-SO_2NH$(C_1-C_4 alkyl) and $-SO_2N$(C_1-C_4 alkyl)(C_1-C_2 alkyl);

-NR^1R^2 or $CR^1R^2R^{10}$ may form a saturated 3 to 8 membered carbocyclic ring which may optionally contain from one to three double bonds and wherein one or two of the ring carbon atoms of such 5 to 8 membered rings may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^3 wherein Z^3 is hydrogen, C_1-C_4 alkyl, benzyl or C_1-C_4 alkanoyl;

R^3 is hydrogen, C_1-C_4 alkyl, -O(C_1-C_4 alkyl), chloro, fluoro, bromo, iodo, -CN, -S(C_1-C_4 alkyl) or $-SO_2$(C_1-C_4 alkyl) wherein each of the (C_1-C_4 alkyl) moieties in the foregoing R^3 groups may optionally be substituted with one substituent R^9 selected from hydroxy, fluoro and (C_1-C_2 alkoxy);

each R^4 is, independently, hydrogen, (C_1-C_6 alkyl), fluoro, chloro, bromo, iodo, hydroxy, cyano, amino, nitro, -O(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl),-S(C_1-C_4 alkyl), -SO(C_1-C_4 alkyl), $-SO_2$(C_1-C_4)alkyl, -CO(C_1-C_4 alkyl), -C(=O)H or -C(=O)O(C_1-C_4alkyl), wherein each of the (C_1-C_6 alkyl) and (C_1-C_4 alkyl) moieties in the foregoing R^4 groups may optionally contain one or two double or triple bonds and may optionally be substituted with one or two substituents independently selected from hydroxy, amino, C_1-C_3 alkoxy, dimethylamino, methylamino, ethylamino, -NHC(=O)CH_3, fluoro, chloro, C_1-C_3 thioalkyl, -CN, -COOH,-C(=O)O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl) and -NO_2;

R^5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, benzoxazolyl or C_3-C_8 cycloalkyl wherein one or two of the carbon atoms of said cycloalkyl rings that contain at least 5 ring members may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^4 wherein Z^4 is hydrogen, C_1-C_4 alkyl or benzyl; and wherein each of the foregoing R^5 groups is substituted with from one to four substituents R^{12} wherein one to three of said substituents may be selected, independently, from chloro, C_1-C_6 alkyl and-O(C_1-C_6 alkyl) and one of said substituents may be selected from bromo, iodo, formyl, -CN, $-CF_3$, $-NO_2$, $-NH_2$, -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_6 alkyl), -C(=O)O(C_1-C_4 alkyl), -C(=O)O(C_1-C_4 alkyl), -COOH, $-SO_2NH$(C_1-C_4 alkyl), $-SO_2N$(C_1-C_2 alkyl)(C_1-C_4 alkyl), $-SO_2NH_2$, $-NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and $-SO_2$(C_1-C_6 alkyl), and wherein each of the C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the foregoing R^5 groups may optionally be substituted with one or two substituents independently selected from fluoro, hydroxy, amino, methylamino, dimethylamino and acetyl;

R^7 is hydrogen, C_1-C_4 alkyl, halo, cyano, hydroxy, -O(C_1-C_4 alkyl) -C(=O)(C_1-C_4 alkyl), -C(=O)O(C_1-C_4alkyl), $-OCF_3$, $-CF_3$, $-CH_2OH$, $-CH_2O$(C_1-C_4, alkyl);

R^{10} is hydrogen, hydroxy, methoxy or fluoro;

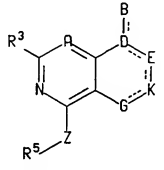
R^{11} is hydrogen or C_1-C_4 alkyl; and

Z is NH, oxygen, sulfur, -N(C_1-C_4 alkyl), -NC(=O)(C_1-C_2 alkyl), NC(=O)O(C_1-C_2alkyl) or $CR^{13}R^{14}$ wherein R^{13} and R^{14} are independently selected from hydrogen, trifluoromethyl and methyl with the exception that one of R^{13} and R^{14}can be cyano;

with the proviso that: (a) in the five membered rings of structures I, II and III, there can not be two double bonds adjacent to each other; and (b) when R^4 is attached to nitrogen, it is not halo, cyano or nitro;

or a pharmaceutically acceptable salt of such compound.

8. The use of claim 2 wherein the corticotropin releasing factor antagonist is a compound of formula



wherein the dashed lines represent optional double bonds;

A is nitrogen or CR^7;

B is $-NR^1R^2$, $-CR^1R^2R^{10}$, $-C(=CR^2R^{11})R^1$, $-NHCR^1R^2R^{10}$, $-OCR^1R^2R^{10}$, $-SCR^1R^2R^{10}$, $-CR^2R^{10}NHR^1$, $-CR^2R^{10}OR^1$, $-CR^2R^{10}SR^1$ or $-COR^2$, and is single bonded to D; or B is $-CR^1R^2$, and is double bonded to D and D is carbon;

D is nitrogen or CR^4 and is single bonded to all atoms to which it is attached, or D is carbon and is double bonded to E or double bonded to B;

E is oxygen, nitrogen, sulfur, C=O, C=S, CR^6R^{12}, NR^6 or CR^6; or E is a two atom spacer, wherein one of the atoms is oxygen, nitrogen, sulfur, C=O, C=S, CR^6R^{12}, NR^6 or CR^6, and the other is CR^6R^{12} or CR^9;

K and G are each, independently, C=O, C=S, sulfur, oxygen, CHR^8 or NR^8 when single bonded to both adjacent ring atoms, or nitrogen or CR^8 when it is double bonded to an adjacent ring atom;

the 6- or 7-membered ring that contains D, E, K and G may contain from one to three double bonds, from zero to two heteroatoms selected from oxygen, nitrogen and sulfur, and from zero to two C=O or C=S groups, wherein the carbon atoms of such groups are part of the ring and the oxygen and sulfur atoms are substituents on the ring;

R^1 is C_1-C_6 alkyl optionally substituted with from one or two substituents independently selected from hydroxy, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, CF_3, $-C(=O)(C_1$-C_4alkyl), $-C(=O)$-O-(C_1-C_4)alkyl, $-OC(=O)(C_1$-C_4 alkyl), $-OC(=O)N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), $-NHCO(C_1$-C_4 alkyl), $-COOH$, $-COO(C_1$-C_4 alkyl), $-CONH(C_1$-C_4 alkyl), $-CON(C_1$-C_4 alkyl)(C_1-C_2 alkyl), $-S(C_1$-C_4 alkyl), $-CN$, $-NO_2$, $-SO(C_1$-C_4 alkyl), $-SO_2(C_1$-C_4 alkyl, $-SO_2NH(C_1$-C_4 alkyl) and $-SO_2N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), wherein each of the C_1-C_4 alkyl groups in the foregoing R^1 groups may optionally contain one or two double or triple bonds;

R^2 is C_1-C_{12} alkyl which may optionally contain from one to three double or triple bonds, aryl or (C_1-C_4 alkylene) aryl, wherein said aryl and the aryl moiety of said (C_1-C_4 alkylene)aryl is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; C_3-C_8 cycloalkyl or (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl), wherein one or two of the carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl may optionally and independently be replaced by an oxygen or sulfur and wherein each of the foregoing R^2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, hydroxy and C_1-C_4 alkyl, or with one substituent selected from C_1-C_6 alkoxy, $-OC(=O)(C_1$-C_6 alkyl), $-OC(=O)N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), $-S(C_1$-C_6 alkyl), amino, $-NH(C_1$-C_2 alkyl), $-N(C_1$-C_2 alkyl)(C_1-C_4 alkyl), $-N(C_1$-C_4 alkyl)-CO-(C_1-C_4 alkyl), $-NHCO(C_1$-C_4 alkyl), $-COOH$, $-COO(C_1$-C_4 alkyl), $-CONH(C_1$-C_4 alkyl), $-CON(C_1$-C_4 alkyl)(C_1-C_2 alkyl), $-SH$, $-CN$, $-NO_2$, $-SO(C_1$-C_4 alkyl), $-SO_2(C_1$-C_4 alkyl), $-SO_2NH(C_1$-C_4 alkyl) and $-SO_2N(C_1$-C_4 alkyl)(C_1-C_2 alkyl);

$-NR1R^2$ or $CR^1R^2R^{10}$ may form a ring selected from saturated 3 to 8 membered rings, the 5 to 8 membered rings of which may optionally contain one or two double bonds, and wherein one or two of the ring carbon atoms of such 5 to 8 membered rings may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^3 wherein Z^3 is hydrogen or C_1-C_4 alkyl;

R^3 is hydrogen, C_1-C_4 alkyl, $-O(C_1$-C_4 alkyl), chloro, fluoro, bromo, iodo, $-S(C_1$-C_4 alkyl) or $-SO_2(C_1$-C_4 alkyl);

R^4 is hydrogen, C_1-C_2 alkyl, hydroxy or fluoro;

each R^6, R^8 and R^9 that is attached to a carbon atom is selected, independently, from hydrogen, C_1-C_2 alkyl, fluoro, chloro, bromo, iodo, hydroxy, hydroxymethyl, formyl, trifluoromethyl, cyano, amino, nitro, -O(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)(C_1-C_2 alkyl), -S(C_1-C_2 alkyl), -CO(C_1-C_2 alkyl), -C(=O)H or -C(=O)O(C_1-C_2 alkyl), wherein each of the C_1-C_2 alkyl moieties in the foregoing R^6, R^8, and R^9 groups may optionally contain one double or triple bond; and each R^6, R^8, and R^9 that is attached to a nitrogen atom is selected, independently, from hydrogen and C_1-C_4 alkyl;

R^5 is substituted phenyl, naphthyl, pyridyl or pyrimidyl, wherein each of the foregoing R^5 groups is substituted with from two to four substituents R^{15}, wherein from one to three of said substituents may be selected, independently, from chloro, C_1-C_6 alkyl, -O(C_1-C_6 alkyl) and -(C_1-C_6alkylene)O(C_1-C_6alkyl), and wherein one of said substituents may be selected, independently, from bromo, iodo, formyl, cyano, trifluoromethyl, nitro, amino, -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_6 alkyl), -C(=O)O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl), -COOH, -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -SO_2NH_2, -$NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and -SO_2(C_1-C_6 alkyl), and wherein each of the C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the foregoing R^5 groups may optionally be substituted with one or two substituents independently selected from fluoro, hydroxy, amino, methylamino, dimethylamino and acetyl;

R^7 is hydrogen, methyl, halo, hydroxy, methoxy, -C(=O)(C_1-C_2 alkyl), -C(=O)O(C_1-C_2 alkyl), trifluoromethoxy, hydroxymethyl, trifluoromethyl or formyl;

R^{10} is hydrogen, hydroxy, methoxy or fluoro;

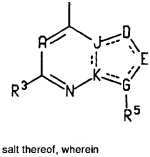
R^{11} is hydrogen or C_1-C_4 alkyl;

R^{12} is hydrogen or methyl; and

Z is NH, oxygen, sulfur, -N(C_1-C_4 alkyl), or $CR^{13}R^{14}$ wherein R^{13} and R^{14} are independently selected from hydrogen, and methyl with the exception that one of R^{13} and R^{14} may optionally be cyano;

with the proviso that: (a) in the six or seven membered rings of structures in formula I, there can not be two double bonds adjacent to each other; and (b) when D is carbon and is double bonded to B, then B is CR^1R^2; or a pharmaceutically acceptable salt of such compound.

9. The use of claim 2 wherein the corticotropin releasing factor antagonist is a compound of formula



or a pharmaceutically acceptable salt thereof, wherein

the dashed lines represent optional double bonds;

A is nitrogen or CR^7;

B is -NR^1R^2, -$CR^1R^2R^{10}$ -C(=CR^2R^{11})R^1, -$NHCR^1R^2R^{10}$, -$OCR^1R^2R^{10}$, -$SCR^1R^2R^{10}$, -$CR^2R^{10}NHR^1$, -$CR^2R^{10}OR^1$, -$CR^2R^{10}SR^1$ or -COR^2;

J and K are each independently nitrogen or carbon and both J and K are not nitrogens;

D and E are each selected, independently, from nitrogen, CR^4, C=O, C=S, sulfur, oxygen, CR^4R^6 and NR^8;

G is nitrogen or carbon;

the ring containing D, E, G, K, and J in formula I may be a saturated or unsaturated 5-membered ring and may optionally contain one or two double bonds and may optionally contain from one to three heteroatoms in the ring and may optionally have one or two C=O or C=S groups;

R^1 is C_1-C_6 alkyl optionally substituted with one or two substituents independently selected from hydroxy, fluoro, chloro, bromo, iodo, -O-(C_1-C_4 alkyl), CF_3, -C(=O)O-(C_1-C_4alkyl), -OC(=O)(C_1-C_4 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -CN, -NO_2, -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl) and -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), wherein each of the C_1-C_4 alkyl groups in the foregoing R^1 groups may optionally contain one or two double or triple bonds;

R^2 is C_1-C_{12} alkyl which may optionally contain from one to three double or triple bonds, aryl or (C_1-C_4 alkylene) aryl, wherein said aryl and the aryl moiety of said (C_1-C_4 alkylene)aryl is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; C_3-C_8 cycloalkyl or (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl), wherein one or two of the carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl) may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^2 wherein Z^2 is selected from hydrogen, C_1-C_4 alkyl, benzyl and C_1-C_4 alkanoyl, and wherein each of the foregoing R^2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, hydroxy and C_1-C_4 alkyl, or with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -OC(=O)(C_1-C_6 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), amino, -NH(C_1-C_6 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)-CO-(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SH, -CN, -NO_2, -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl) and -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl); -NR^1R^2 or $CR^1R^2R^{10}$ may form a saturated 3 to 8 membered carbocyclic ring which may optionally contain from one to three double bonds and wherein one or two of the ring carbon atoms of such 5 to 8 membered rings may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^3 wherein Z^3 is hydrogen, C_1-C_4 alkyl, benzyl or C_1-C_4 alkanoyl;

R^3 is hydrogen, C_1-C_4 alkyl, -O(C_1-C_4 alkyl), chloro, fluoro, bromo, iodo, (C_1-C_2 alkylene)-O-(C_1-C_2 alkyl), (C_1-C_2 alkylene)-OH, or -S(C_1-C_4 alkyl);

each R^4 is, independently, hydrogen, (C_1-C_6 alkyl), fluoro, chloro, bromo, iodo, hydroxy, cyano, amino, (C_1-C_2 alkylene)-OH, CF_3, CH_2SCH_3, nitro, -O(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -C(=O)H or -C(=O)O(C_1-C_4alkyl);

R^6 is hydrogen, methyl or ethyl;

R^8 is hydrogen or C_1-C_4 alkyl;

R^5 is phenyl, pyridyl, pyrazinyl, pyrimidyl, pyridazinyl and wherein each of the foregoing R^5 groups is substituted with from one to four substituents R^{13} wherein one to three of said substituents may be selected, independently, from fluoro, chloro, C_1-C_6 alkyl and -O(C_1-C_6 alkyl) and one of said substituents may be selected from bromo, iodo, formyl, OH, (C_1-C_4 alkylene)-OH, (C_1-C_4alkylene)-O-(C_1-C_2 alkyl), -CN, -CF_3, -NO_2, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -OCO(C_1-C_4 alkyl), (C_1-C_4 alkylene)-O-(C_1-C_4 alkyl), -S(C_1-C_6 alkyl), (C_1-C_4 alkylene)-S-(C_1-C_4 alkyl), -C(=O)O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl), -COOH, -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -SO_2NH_2, -$NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and -SO_2(C_1-C_6 alkyl), and wherein each of the C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the foregoing R^5 groups may optionally have one or two double bonds;

R^7 is hydrogen, C_1-C_4 alkyl, halo (e.g., chloro, fluoro, iodo or bromo), hydroxy, -O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl), -C(=O)O(C_1-C_4 alkyl), -OCF_3, -CF_3, -CH_2OH or -CH_2O(C_1-C_2 alkyl);

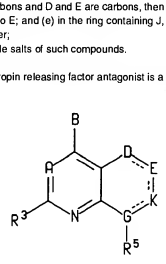
R^{10} is hydrogen, hydroxy, methoxy or fluoro;

R^{11} is hydrogen or C_1-C_4 alkyl; and

with the proviso that: a) when both J and K are carbons and D is CR^4 and E is nitrogen, then G can not be nitrogen; (b) when both J and K are carbons and D and G are nitrogens, then E can not be CR^4 or C=O or C=S; (c) when both J and K are carbons and D and E are carbons, then G can not be nitrogen; (d) when G is carbon, it must be double banded to E; and (e) in the ring containing J, K, D, E and G, there can not be two double bonds adjacent to each other;

and the pharmaceutically acceptable salts of such compounds.

10. The use of claim 2 wherein the corticotropin releasing factor antagonist is a compound of formula

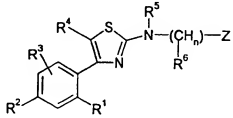


wherein the dashed lines represent optional double bonds;

A is nitrogen or CR^7;
B is -NR^1R^2, -$CR^1R^2R^{10}$, -$C(=CR^2R^{11})R^1$, -$NHCR^1R^2R^{10}$, -$OCR^1R^2R^{10}$, -$SCR^1R^2R^{10}$, -$CR^2R^{10}NHR^1$, -$CR^2R^{10}OR^1$, -$CR^2R^{10}SR^1$ or -COR^2;
G is nitrogen or CR^4 and is single bonded to all atoms to which it is attached, or G is carbon and is double bonded to K;
K is nitrogen or CR^6 when double bonded to G or E, or K is oxygen, sulfur, C=O, C=S, CR^6R^{12} or NR^8 when single bonded to both adjacent ring atoms, or K is a two atom spacer, wherein one of the two ring atoms of the spacer is oxygen, nitrogen, sulfur, C=O, C=S, CR^6R^{12}, NR^6 or CR^6, and the other is CR^6R^{12} or CR^9;
D and E are each, independently, C=O, C=S, sulfur, oxygen, CR^4R^6 or NR^8 when single bonded to both adjacent ring atoms, or nitrogen or CR^4 when it is double bonded to an adjacent ring atom;
the 6- or 7-membered ring that contains D, E, K and G may contain from one to three double bonds, from zero to two heteroatoms selected from oxygen, nitrogen and sulfur, and from zero to two C=O or C=S groups, wherein the carbon atoms of such groups are part of the ring and the oxygen and sulfur atoms are substituents on the ring;
R^1 is C_1-C_6 alkyl optionally substituted with from one or two substituents independently selected from hydroxy, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, CF_3, -C(=O)(C_1-C_4alkyl), -C(=O)-O-(C_1-C_4)alkyl, -OC(=O)(C_1-C_4 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -CN, -NO_2, -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl) and -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), wherein each of the C_1-C_4 alkyl groups in the foregoing R^1 groups may optionally contain one or two double or triple bonds;
R^2 is C_1-C_{12} alkyl which may optionally contain from one to three double or triple bonds, aryl or (C_1-C_4 alkylene) aryl, wherein said aryl and the aryl moiety of said (C_1-C_4 alkylene)aryl is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; C_3-C_8 cycloalkyl or (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl), wherein one or two of the carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl may optionally and independently be replaced by an oxygen or sulfur atom or by NZ wherein Z is hydrogen, C_1-C_4 alkyl or benzyl, and wherein each of the foregoing R^2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, hydroxy and C_1-C_4 alkyl, or with one substituent selected from C_1-C_6 alkoxy, -OC(=O)(C_1-C_6 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), amino, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)-CO-(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SH, -CN, -NO_2, -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl) and -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl);
-NR^1R^2 or $CR^1R^2R^{10}$ may form a ring selected from saturated 3 to 8 membered rings, the 5 to 8 membered rings of which may optionally contain one or two double bonds, and wherein one or two of the ring carbon atoms of such 5 to 8 membered rings may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^2 wherein Z^2 is hydrogen, benzyl or C_1-C_4 alkyl;
R^3 is hydrogen, C_1-C_4 alkyl, -O(C_1-C_4 alkyl), chloro, fluoro, bromo, iodo, -S(C_1-C_4 alkyl) or -SO_2(C_1-C_4 alkyl); each R^8, R^9 and R^{12} is selected, independently, from hydrogen and C_1-C_2 alkyl;
each R^4 and R^6 that is attached to a carbon atom is selected, independently, from hydrogen and C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, hydroxy, hydroxy (C_1-C_2 alkyl), trifluoromethyl, cyano, amino, nitro, -O(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -CH_2SCH_3, -S(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -C(=O)H or -C(=O)O(C_1-C_4 alkyl), wherein each of the C_1-C_2 alkyl moieties in the foregoing R^4 and R^6 groups may optionally contain one double or triple bond; and R^6, when attached to a nitrogen atom, is selected from hydrogen and C_1-C_4 alkyl;
R^5 is substituted phenyl, naphthyl, pyridyl or pyrimidyl, wherein each of the foregoing R^5 groups is substituted with from two to four substituents R^{13}, wherein up to three of said substituents may be selected, independently, from chloro, C_1-C_6 alkyl, -O(C_1-C_6 alkyl) and -(C_1-C_6 alkylene)O(C_1-C_6alkyl), and wherein one of said substituents may be selected, independently, from bromo, iodo, formyl, cyano, trifluoromethyl, nitro, amino, -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_6 alkyl), -C(=O)O(C$_1$-C$_4$ alkyl), -C(=O)(C_1-C_4 alkyl), -COOH, -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -SO_2NH$_2$, -$NHSO_2$(C_1-C_4 alkyl), -(C_6-C_1alkylene)-S-(C_1-C_2alkyl), -(C_6-C_1alkylene)-SO-(C_1-C_2alkyl), -(C_6-C_1alkylene)-SO_2-(C_1-C_2alkyl) and -(C_1-C_4alkylene)-OH, and wherein each of the C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the foregoing R^5 groups may optionally be substituted with one or two substituents independently selected from fluoro, hydroxy, amino, methylamino, dimethylamino and acetyl;
R^7 is hydrogen, methyl, halo (e.g., chloro, fluoro, iodo or bromo), hydroxy, methoxy, -C(=O)(C_1-C_2 alkyl), -C(=O)O(C_1-C_2 alkyl), hydroxymethyl, trifluoromethyl or formyl;

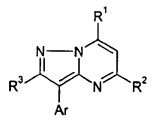
R^{10} is hydrogen, hydroxy, methoxy or fluoro; and
R^{11} is hydrogen or C_1-C_4 alkyl;
with the proviso that in the ring containing D, E, K and G of formula I, there can not be two double bonds adjacent to each other;
and the pharmaceutically acceptable salt of such compound.

11. The use of claim 2 wherein the corticotropin releasing factor antagonist is a compound of formula



wherein each of R^1 and R^2 is independently a halogen atom; a C_1-C_5 hydroxyalkyl radical; C_1-C_5 alkyl; C_7-C_{10} aralkyl; C_1-C_5 alkoxy; trifluoromethyl; nitro; nitrile; a group -SR where R is hydrogen, a C_1-C_5 alkyl radical or a C_7-C_{10} aralkyl radical; a group S-CO-R where R is a C_1-C_5 alkyl radical or aralkyl in which the aryl portion is C_6-C_8 and the alkyl portion is C_1-C_4; a group -COOR' where R' is hydrogen or C_1-C_5 alkyl; a group -CONR'R" where R' and R" are as defined above for R'; a group -NR'R" where R' and R" are as previously defined for R'; a group-CONRaRb or NRaRb, where Ra and Rb, taken together with the nitrogen atom to which they are attached, form a 5- to 7-membered heterocyclic ring; or a group-NHCO-NR'R", where R' and R" are as defined above for R"; R^3 is hydrogen or as defined for R^1 and R^2 is a hydrogen atom; C_{1-5} alkyl; halogen; a hydroxymethyl group; or a formyl group; R^5 is C_1-C_5 alkyl; a C_3-C_7 cycloalkyl group; a cycloalkylalkyl group in which the cycloalkyl portion is C_3-C_7 and the alkyl portion is C_1-C_5; or C_5-C_6 alkenyl; n is 0 or 1; R^6 is C_{1-5} alkyl; alkoxyalkyl in which the alkyl portions are C_1-C_3, C_3-C_7 cycloalkyl; a cycloalkylalkyl group in which the cycloalkyl portion is C_3-C_7 and the alkyl portion is C_1-C_5; a cycloalkyloxyalkyl radical in which the cycloalkyl is C_3-C_7 and the alkyl is C_1-C_4; a hydroxyalkyloxyalkyl radical in which the alkyls are C_2-C_{10}; or an alkoxyalkyloxyalkyl radical in which the alkyls are C_3-C_{12}; and Z is an optionally substituted bi- or tricyclic aromatic or heteroaromatic group; and stereoisomers and/or addition salts thereof.

12. The use of claim 2 wherein the corticotropin releasing factor antagonist is a compound of formula



including the stereoisomers and the pharmaceutically acceptable acid addition salt forms thereof, wherein

R^1 is NR^4R^5 or OR^5;
R^2 is C_1-C_6alkyl, C_1-C_6alkyloxy or C_1-C_6alkylthio,
R^3 is hydrogen, C_1-C_6alkyl, C_1-C_6alkylsulfonyl, C_1-C_6alkylsulfoxy or C_1-C_6alkylthio;
R^4 is hydrogen, C_1-C_6alkyl, mono- or di(C_3-C_6cycloalkylmethyl, C_3-C_6cycloalkyl, C_3-C_6alkenyl, hydroxyC_1-C_6alkyl, C_1-C_6alkylcarbonyloxyC_1-C_6alkyl or C_1-C_6alkyloxyC_1-C_6alkyl;
R^5 is C_1-C_6alkyl, mono- or di(C_3-C_6cycloalkyl)methyl, Ar^1CH_2, C_3-C_6alkenyl, C_1-C_6alkyloxyC_1-C_6alkyl, hydroxyC_1-C_6alkyl, thienylmethyl, furanylmethyl, C_1-C_6alkylthioC_1-C_6alkyl, morpholinyl, mono- or di(C_1-C_6alkyl)aminoC_1-C_6alkyl, di(C_1-C_6alkyl)amino, C_1-C_6alkylcarbonylC_1-C_6alkyl, C_1-C_6alkyl substituted with imidazolyl; or a radical of formula -Alk-O-CO-Ar^1;

or R^4 and R^5 taken together with the nitrogen atom to which they are attached may form a pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group, optionally substituted with C_1-C_6alkyl or C_1-C_6alkyloxyC_1-C_6alkyl; and

Ar is phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from halo, C_1-C_6alkyl, trifluoromethyl, hydroxy, cyano, C_1-C_6alkyloxy, benzyloxy, C_1-C_6alkylthio, nitro, amino and mono- or di(C_1-C_6alkyl)amino; pyridinyl; pyridinyl substituted with 1 ~ 2 or 3 substituents independently selected from halo, C_1-C_6alkyl, trifluoromethyl, hydroxy, cyano, C_1-C_6alkyloxy, benzyloxy, C_1-C_6alkylthio, nitro, amino, mono- or di(C_1-C_6alkyl)amino and piperidinyl; and wherein said substituted phenyl may optionally be further substituted with one or more halogens;

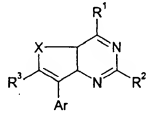
Ar^1 is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C_1-C_6alkyl, C_1-C_6alkyloxy, di(C_1-C_6alkyl)aminoC_1-C_6alkyl, trifluoromethyl and C_1-C_6alkyl substituted with morpholinyl; or pyridinyl; and Alk is C_1-C_6alkanediyl;

with the proviso that

5-methyl-3-phenyl-7-(phenylmethoxy)-pyrazolo[1,5-a]-pyrimidine and

2,5-dimethyl-7-(methylamino)-3-phenyl-pyrazolo[1,5-a]pyrimidine are not included.

13. The use of claim 2 wherein the corticotropin releasing factor antagonist is a compound of formula



including the stereoisomers and the pharmaceutically acceptable acid addition salt forms thereof, wherein

X is S, SO or SO_2;

R1 is NR^4R^5 or OR^5;

R^2 is C_1-C_6alkyl, C_1-C_6alkyloxy or C_1-C_6alkylthio;

R^3 is hydrogen, C_1-C_6alkyl, C_1-C_6alkylsulfonyl, C_1-C_6alkylsulfoxy or C_1-C_6alkylthio;

R^4 is hydrogen, C_{1-6}alkyl, mono- or di(C_3-C_6cycloalkyl)methyl, C_3-C_6cycloalkyl, C_3-C_6alkenyl, hydroxyC_1-C_6alkyl, C_1-C_6alkylcarbonyloxyC_1-C_6alkyl or C_1-C_6alkyloxyC_1-C_6alkyl;

R^5 is C_1-C_6alkyl, mono- or di(C_3-C_6cycloalkyl)methyl, Ar^1CH_2, C_3-C_6alkenyl, C_1-C_6alkyloxyC_1-C_6alkyl, hydroxyC_1-C_6alkyl, thienylmethyl, furanylmethyl, C_1-C_6alkylthioC_1-C_6alkyl, morpholinyl, mono- or di(C_1-C_6alkyl)aminoC_1-C_6alkyl, di(C_1-C_6alkyl)amino, C_1-C_6alkylcarbonylC_1-C_6alkyl, C_1-C_6alkyl substituted with imidazolyl; or a radical of formula -Alk-O-CO-Ar ;

or R^4 and R^5 taken together with the nitrogen atom to which they are attached may form a pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group, optionally substituted with C_1-C_6alkyl or C_1-C_6alkyloxyC_1-C_6alkyl;

Ar is phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from halo, C_1-C_6alkyl, trifluoromethyl, hydroxy, cyano, C_1-C_6alkyloxy, benzyloxy, C_1-C_6alkylthio, nitro, amino and mono- or di(C_1-C_6alkyl)amino; pyridinyl; pyridinyl substituted with 1, 2 or 3 substituents independently selected from halo, C_1-C_6alkyl, trifluoromethyl, hydroxy, cyano, C_1-C_6alkyloxy, benzyloxy, C_1-C_6alkylthio, nitro, amino, mono- or di(C_1-C_6alkyl)amino and piperidinyl; and wherein said substituted phenyl may optionally be further substituted with one or more halogens;

$Ar^1$is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C_1-C_6alkyl, C_1-C_6alkyloxy, di(C_1-C_6alkyl)aminoC_1-C_6alkyl trifluoromethyl, and C_1-C_6alkyl substituted with morpholinyl; or pyridinyl; and

Alk is C_1-C_6alkanediyl.

14. The use of claim 2 wherein the corticotropin releasing factor antagonist is a compound selected from the group consisting of:

4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-pyridine;
butyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]-ethyl-amine;
4-(butyl-ethylamino)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one;
4-(1-ethylpropoxy)-2,5-dimethyl-6-(2,4,6-trimethylphenoxy)-pyrimidine;
N-butyl-N-ethyl-2,5-dimethyl-NN-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine;
[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yl]-(2,4,6-trimethylphenyl)-amine;
6-(ethyl-propyl-amino)-2,7-dimethyl-9-(2,4,6-trimethylphenyl)-7,9-dihydro-purin-8-one;
3-[(4-methyl-benzyl)-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino]-propan-1-ol;
diethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
2-[butyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino]-ethanol;
dibutyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
butyl-ethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
butyl-ethyl-[6-methyl-3-methylsulfonyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
butyl-cyclopropylmethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1 H-pyrazolo[3,4-d]pylimidin-4-yl]-amine;
di-1-propyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
diallyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
butyl-ethyl-[6-chloro-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
butyl-ethyl-[6-methoxy-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
propyl-ethyl-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
4-(1-ethyl-propyl)-6-methyl-3-methylsulfanyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidine;
n-butyl-ethyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
di-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
ethyl-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
diethyl-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
n-butyl-ethyl-[2,5,6-trimethyl-7-(2,4,6-trimethyl phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
2-[N-n-butyl-N-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-ethanol;
4-(1-ethyl-propyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine;
n-butyl-ethyl-[2,5-dimethyl-7-(2,4-dimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidyl-4-yl]-(1-ethyl-propyl)amine;
butyl-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyddin-4-yl]-ethylamine;
[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4,b]pyridin-4-yl]-(1-methoxymethylpropyl)-amine;
4-(1-methoxymethylpropoxy)-3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridine;
(1-ethylpropyl)-[3,5,6-trimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl]-amine;
4-(1-ethylpropoxy)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-b]pyridine;
4-(1-ethylpropoxy)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-b]pyridine;
4-(1-ethylpropoxy)-2,5-dimethyl-7-(2,6-dimethyl-4-bromophenyl)-7H-pyrrolo[2,3-b]pyridine;
2,5,6-trimethyl-7-(1-propylbutyl)-4-(2,4,6-trimethylphenoxy)-7H-pyrrolo[2,3-d]pyrimidine;
1-(1-ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenylamino)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
9-(1-ethylpropyl)-2-methyl-6-(2,4,6-trimethylphenylamino)-7,9-dihydro-purin-8-one;
1-(1-ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenoxy)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
1-(1-ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenoxy)-1H-imidazo[4,5-c]pyridine;
1-(1-ethylpropyl)-3,6-dimethyl-4-(2,4,6-trimethylphenoxy)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
1-(1-ethylpropyl)-3,6-dimethyl-4-(2,4,6-trimethylphenylamino)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
1-(1-ethyl-propyl)-4,7-dimethyl-5-(2,4,6-trimethyl-phenoxy)-1,4-dihydro-2H-pyrido[3,4-b]pyrazin-3-one;
1-(1-ethyl-propyl)-4,7-dimethyl-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetrahydro-pyrido[3,4-b]pyrazine;
1-(1-ethyl-propyl)-7-methyl-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetrahydro-pyrido[3,4-b]pyrazine;
1-(1-ethyl-propyl)-7-methyl-2-oxo-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetra-hydro-[1,6]naphthyridine-3-carboxylic acid methyl ester;
1-(1-ethyl-propyl)-7-methyl-2-oxo-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetra-hydro-[1,6]naphthyridine-3-carboxylic acid isopropyl ester;
1-(1-ethyl-propyl)-7-methyl-5-(2,4,6-trimethyl-phenoxy)-3,4-dihydro-1H-[1,6]naphthyridin-2-one;
1-(1-ethyl-propyl)-7-methyl-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetrahydro-[1,6]naphthyridine;
1-(1-ethyl-propyl)-7-methyl-5-(2,4,6-trimethyl-phenoxy)-1,4-dihydro-2H-3-oxa-1,6-diaza-naphthalene;
1-(1-ethyl-propyl)-4,7-dimethyl-5-(2,4,6-trimethyl-phenoxy)-1,4-dihydro-2H-3-oxa-1,6-diaza-naphthalene;
1-(1-ethyl-propyl)-3,7-dimethyl-5-(2,4,6-trimethyl-phenoxy)-3,4-dihydro-1H-3-oxa-[1,6]-naphthyridin-2-one;

1-(1-ethyl-propyl)-3,3,6-trimethyl-4-(2,4,6-trimethyl-phenoxy)-2,3-dihydro-1 H-pyrrolo[3,2-c]pyridine;
7-(1-ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidine;
[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-(1-ethyl-propyl)-amine;
(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-amine;
7-(1-ethyl-propoxy)-2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidine;
[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-ethylpropyl-amine;
[6-bromo-5-bromomethyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-(1-ethyl-propyl)-amine;
(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-amine;
[6-bromo-5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-(1-ethyl-propyl)-methyl-amine;
7-(1-ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridine;
4-(1-ethyl-propoxy)-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine;
(±)-2,5-dimethyl-4-(tetrahydro-furan-3-yloxy)-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo-[3,2-d]pyrimidine;
2,5-dimethyl-4-(S)-(tetrahydro-furan-3-yloxy)-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo-[3,2-d]pyrimidine;
2,5-dimethyl-4-(1-propyl-butoxy)-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine;
4-sec-butylsulfanyl-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine;
4-(butyl-ethyl-amino)-2,6-dimethyl-8-(2,4,6-trimethyl-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;
8-(1-ethyl-propoxy)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido[2,3-b] pyrazin-2-one;
8-(1-ethyl-propoxy)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido [2,3-b]pyrazine;
4-(1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;
5-(1-ethyl-propoxy)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;
5-(1-ethyl-propoxy)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,2-dihydro-3-oxa-1,8-diaza-naphthalen-4-one;
8-(1-ethyl-propoxy)-1,6-dimethyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;
(1-ethyl-propyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-quinolin-4-yl]-amine;
4-(butyl-ethyl-amino)-2,6-dimethyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;
4-(butyl-ethyl-amino)-2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;
4-(1-ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;
(butyl-ethyl)-[2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidin-4-yl]-amine;
(propyl-ethyl)-[2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidin-4-yl]-amine;
(diethyl)-[2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,6,7,8-tetrahydro-pyrido [2,3-d]pyrimidin-4-yl]-amine;
(1-ethyl-propyl)-[2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidin-4-yl]-amine;
(1-ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidine;
4-(butyl-ethyl-amino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;
4-(1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-5,8-dihydro-6H-pyrido [2,3-d]pyrimidin-7-one;
(butyl-ethyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2, 3-d] pyrimidin-4-yl]-amine;
(propyl-ethyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-pyrido-[2,3-d] pyrimidin-4-yl]-amine;
(diethyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d] pyrimidin-4-yl]-amine;
(1-ethyl-propyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydropyrido[2,3-d] pyrimidin-4-yl]-amine;
(1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydropyrido[2,3-d] pyrimidine;
8-(1-ethyl-propoxy)-6-methyl-4-(2,6-dimethyl-4-bromo-phenyl)-3,4-dihydro-1H-pyrido [2,3-b]pyrazin-2-one;
8-(1-ethyl-propoxy)-6-methyl-4-(2,6-dimethyl-4-bromo-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;
4-(1-ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-quinoline;
5-(1-ethyl-propoxy)-7-methyl-1-(2,6-dimethyl-4-bromo-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;
5-(1-ethyl-propoxy)-7-methyl-1-(2,6-dimethyl-4-bromo-phenyl)-1,2-dihydro-3-oxa-1,8-diaza-naphthalen-4-one;
8-(1-ethyl-propoxy)-1,6-dimethyl-4-(2,6-dimethyl-4-bromo-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;
(1-ethyl-propyl)-[2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-quinolin-4-yl]-amine;
4-(butyl-ethyl-amino)-2,6-dimethyl-8-(2,6-dimethyl-4-chloro-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;
8-(1-ethyl-propoxy)-6-methyl-4-(2,6-dimethyl-4-chloro-phenyl)-3,4-dihydro-1 H- pyrido[2,3-b]pyrazin-2-one;

8-(1-ethyl-propoxy)-6-methyl-4-(2,6-dimethyl-4-chloro-phenyl)-1,2,3,4-tetrahydro- pyrido[2,3-b]pyrazine;
4-(1-ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-chloro-phenyl)-quinoline; 5-(1-ethyl-propoxy)-7-methyl-1-(2,6-dimethyl-4-chloro-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;
5-(1-ethyl-propoxy)-7-methyl-1-(2,6-dimethyl-4-chloro-phenyl)-1,2-dihydro-3-oxa-1,8-diaza-naphthalen-4-one;
8-(1-ethyl-propoxy)-1,6-dimethyl-4-(2,6-dimethyl-4-chloro-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;
(1-ethyl-propyl)-[2-methyl-8-(2,6-dimethyl-4-chloro-phenyl)-quinolin-4-yl]-amine;
8-(1-hydroxymethyl-propoxy)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro - 1H-pyrido[2,3-b]pyrazin-2-one;
8-(1-hydroxymethyl-propylamino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido[2,3-b]pyrazin-2-one;
8-(1-ethyl-propylamino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido[2,3-b]pyrazin-2-one;
8-diethylamino-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido-[2,3-b] pyrazin-2-one;
8-(ethyl-propyl-amino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido[2,3-b]pyrazin-2-one;
8-(butyl-ethyl-amino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido [2,3-b]pyrazin-2-one;
8-(1-hydroxymethyl-propoxy)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;
8-(1-hydroxymethyl-propylamino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4 - tetrahydro-pyrido[2,3-b]pyrazine;
8-(1-ethyl-propylamino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;
8-diethylamino-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;
8-(ethyl-propyl-amino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro - pyrido[2,3-b]pyrazine;
8-(butyl-ethyl-amino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine;
4-(1-hydroxymethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;
4-(1-hydroxymethyl-propylamino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;
4-(1-ethyl-propylamino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;
4-diethylamino-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;
4-(ethyl-propyl-amino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;
4-(butyl-ethyl-amino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;
5-(1-hydroxymethyl-propoxy)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro - 2H-3-oxa-1,8-diaza-naphthalene;
5-(1-hydroxymethyl-propylamino)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3- oxa-1,8-diaza-naphthalene;
5-(1-ethyl-propylamino)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3- oxa-1,8-diaza-naphthalene;
5-diethylamino-5-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-oxa-1,8 - diaza-naphthalene;
5-(ethyl-propyl-amino)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;
8-(butyl-ethyl-amino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;
4-(2,4-dichlorophenyl)-5-methyl-2-[N-(1-(methoxymethyl)-1-(naphth-2-yl) methyl)-N-propylamino]thiazole;
oxalate of 4-(2,4-dichlorophenyl)-5-methyl-2-[N-(6-methoxyisoquinol-5-yl)-N-propylamino]thiazole;
oxalate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(6-methylisoquinol-5 -yl)-N-propylamino]thiazole;
4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(1-methoxycarbonylmethylindol - 5-yl)-N-propylamino]thiazole;
oxalate of -(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(6-methoxyisoquinol-5-yl)-N-propylamino]thiazole;
oxalate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(6-chloroisoquinol-5 -yl)-N- propylamino]thiazole;
oxalate of -(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(6-methoxyisoquinol-5 -yl)-N- propylamino]thiazole;
4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-1-methoxynaphth-2-yl)-N-propylamino]thiazole;
oxalate of 4-(2-chloro-4-trifluoromethylphenyl)-5-methyl-2-[N-(6-methoxyisoquinol-5-yl)-N-propylamino]thiazole;
chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(2-ethoxynaphth-1-yl)-N- propylamino]thiazole;
chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2[N-(2,3-dimethylnaphth-1-yl)-N-propylamino]thiazole;
chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(6-bromo-2-methoxynaphth-1-yl)-N-propylamino]thiazole;
chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(2,6-dimethylnaphth-1-yl)-N-propylamino]thiazole;
chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(1-(methoxymethyl)-1-(naphth-2-yl)methyl)-N-propylamino]thiazole;
chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(1-(cyclopropyl)- 1-(naphth-2-yl)methyl)-N-propylamino]thiazole;
3-(2,4-dichlorophenyl)-5-methyl-7(N-propyl-N-cyclopropanemethylamino)-pyrazolo[2,3-a]pyrimidine;

3-(2,4-dichlorophenyl)-5-methyl-7-(N-allyl-N-cyclopropanemethylamino)-pyrazolo[2,3-a]pyrimidine;
2-methylthio-3-(2,4-dichlorophenyl)-5-methyl-7-(N,N-diallylamino)pyrazolo[2,3-a]pyrimidine;
2-methylthio-3-(2,4-dichlorophenyl)-5-methyl-7-(N-butyl-N-cyclopropanemethyl-amino)pyrazolo[2,3-a]pyrimidine;
2-methylthio-3-(2,4-dichlorophenyl)-5-methyl-7-(N-propyl-N-cyclopropanemethyl-amino)pyrazolo[2,3-a]pyrimidine;
2-methyl-3-(4-chlorophenyl)-5-methyl-7-(N,N-dipropylamino)-pyrazolo[2,3-a] pyrimidine;
3-[6-(dimethylamino)-3-pyridinyl-2,5-dimethyl-N,N-dipropylpyrazolo[2,3-a] pyrimidin-7-amine;
3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-N,N-dipropyl-pyrazolo[2,3-a]pyrimidine-7-amine;
3-(2,4-dimethoxyphenyl)-2,5-dimethyl-7-(N-propyl-N-methyloxyethylamino)pyrazolo[2,3-a)pyrimidine;
7-(N-diethylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl-[1,5-a]-pyrazolopyrimidine;
7-(N-(3-cyanopropyl)-N-propylamino-2,5,dimethyl-3-(2,4-dimethylphenyl)-[1,5-a]-pyrazolopyrimIdine;
[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-(-ethyl-propyl)-amine;
[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-(1-ethylpropyl)-amine;
cyclopropylmethyl-[3-(2,4-dimethyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl)-propyl-amine;
cyclopropylmethyl-[3-(2-methyl-4-chloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-propyl-amine;
cyclopropylmethyl-[3-(2,4-di-chloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-propyl-amine;
[3-(2-methyl-4-chloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-di-propyl-amine;
[2,5-dimethyl-3-(2,4-dimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-(1-ethylpropyl)-amine;
[2,5-dimethyl-3-(2,4-dichloro-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-(1-ethylpropyl)-amine;
4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester;
3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-N-propyl-N-cyclopropylmethyl-pyrazolo[2,3-a]pyrimidin-7-amine; and
3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-N-ethyl-N-cyclopropylmethyl-pyrazolo[2,3-a]pyrimidin-7-amine.

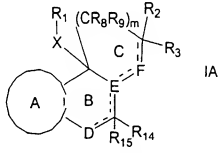
15. The use of claim 2 wherein the corticotropin releasing factor antagonist is a compound selected from the group consisting of:

4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-pyridine;
4-(1-ethylpropoxy)-2,5-dimethyl-6-(2,4,6-trimethylphenoxy)-pyrimidine;
[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yl]-(2,4,6-trimethylphenyl)-amine;
3-{(4-methyl-benzyl)-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propan-1-ol;
propyl-ethyl-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
ethyl-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
2-{N-n-butyl-N-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}-ethanol;
[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4,b]pyridin-4-yl]-(1-methoxymethylpropyl)-amine;
4-(1-ethylpropoxy)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2, 3-b]pyridine;
2,5,6-trimethyl-7-(1-propylbutyl)-4-(2,4,6-trimethylphenoxy)-7H-pyrrolo[2,3-d]pyrimidine;
1-(1-ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenoxy)-1,3-dihydroimidazo[4,5-c]pyridin-2-one;
1-(1-ethyl-propyl)-4,7-dimethyl-5-(2,4,6-trimethyl-phenoxy)-1,4-dihydro-2H-pyrido[3,4-b]pyrazin-3-one;
1-(1-ethyl-propyl)-4,7-dimethyl-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetrahydro-pyrido[3,4-b]pyrazine;
1-(1-ethyl-propyl)-7-methyl-2-oxo-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetrahydro-[1,6]naphthyridine-3-carboxylic acid isopropyl ester;
1-(1-ethyl-propyl)-7-methyl-5-(2,4,6-trimethyl-phenoxy)-1,4-dihydro-2H-3-oxa-1,6-diaza-naphthalene;
(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-amine;
7-(1-ethyl-propoxy)-2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidine;
4-(1-ethyl-propoxy)-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine;
4-(butyl-ethyl-amino)-2,6-dimethyl-8-(2,4,6-trimethyl-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;
8-(1-ethyl-propoxy)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydropyrido [2,3-b]pyrazine;
4-(1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;
(1-ethyl-propyl-)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-quinolin-4-yl]-amine;
(propyl-ethyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-pyrido-[2,3-d] pyrimidin-4-yl]-amine;
(1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydropyrido[2,3-d] pyrimidine;
8-(1-hydroxymethyl-propylamino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido[2,3-b]pyrazin-2-one;

4-(1-hydroxymethyl-propylamino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;
5-(1-hydroxymethyl-propylamino)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;
[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-(1-ethyl-propyl)-amine;
cyclopropylmethyl-[3-(2,4-dimethyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-propyl-amine;
[2,5-dimethyl-3-(2,4-dimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-(1-ethylpropyl)-amine;
3-[6-(dimethylamino)-3-pyridinyl-2,5-dimethyl-N,N-dipropylpyrazolo[2,3-a] pyrimidin-7-amine;
3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-N,N-dipropylpyrazolo[2,3-a]pyrimidine-7-amine;
3-(2,4-dimethoxyphenyl)-2,5-dimethyl-7-(N-propyl-N-methyloxyethylamino)-pyrazolo(2,3-a)pyrimidine;
7-(N-diethylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl-[1,5-a]-pyrazolopyrimidine; and
7-(N-(3-cyanopropyl)-N-propylamino-2,5,dimethyl-3-(2,4-dimethylphenyl)-[1,5-a]-pyrazolopyrimidine.

16. The use of claim 1 which further comprises administering to said animal an amount of a glucocorticoid receptor antagonist;
wherein the amount of the corticotropin releasing factor antagonist and the amount of the glucocorticoid receptor antagonist result in a therapeutic effect.

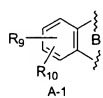
17. The use of claim 16 wherein the glucocorticoid receptor antagonist is a compound of formula IA



IA

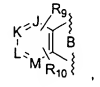
an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug; wherein m is 1 or 2;
- - - represents an optional bond;

A is selected from the group consisting of



A-1

A-2



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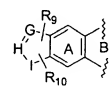
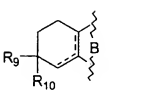


A-4

and



A-5

D is CR_7, CR_7R_{16}, N, NR7 or O;
E is C, CR_8 or N;
F is CR_4, CR_4R_5 or O;
G, H and I together with 2 carbon atoms from the A-ring or 2 carbon atoms from the B-ring form a 5-membered heterocyclic ring comprising one or more N, O or S atoms; provided that there is at most one of O and S per ring;
J, K, L and M together with 2 carbon atoms from the B-ring forms a 6-membered heterocyclic ring comprising 1 or more N atoms;
X is a) absent, b) $-CH_2-$, c) -CH(OH)- or d) -C(O)-;
R_1 is a) -H, b) -Z-CF_3, c) -(C_1-C_6)alkyl, d) -(C_2-C_6)alkenyl, e) -(C_2-C_6)alkynyl, f) -CHO, g) -CH=N-OR_{12}, h) -Z-C(O)OR_{12}, i) -Z-C(O)-$NR_{12}R_{13}$, j) -Z-C(O)-NR_{12}-Z-het, k) -Z-$NR_{12}R_{13}$, l) -Z-NR_{12}het, m) -Z-het, n) -Z-O-het, o) -Z-aryl', p) -Z-O-aryl', q) -CHOH-aryl' or r) -C(O)-aryl' wherein aryl' in substituents o) to r) is substituted independently with 0, 1 or 2 of the following: -Z-OH, -Z-$NR_{12}R_{13}$, -Z-NR_{12}-het, -C(O)$NR_{12}R_{13}$, -C(O)O(C_1-C_6)alkyl, -C(O)OH, -C(O)-het, -NR_{12}-C(O)-(C_1-C_6)alkyl, -NR_{12}-C(O)-(C_2-C_6)alkenyl, -NR_{12}-C(O)-(C_2-C_6)alkynyl, -NR_{12}-C(O)-Z-het, -CN, -Z-het, -O-(C_1-C_3)alkyl-C(O)-$NR_{12}R_{13}$, -O-(C_1-C_3)alkyl-C(O)O(C_1-C_6)alkyl, -NR_{12}-Z-C(O)O(C_1-C_6)alkyl, -N(Z-C(O)O(C_1-C_6)alkyl)$_2$, -NR_{12}-Z-C(O)-$NR_{12}R_{13}$, -Z-NR_{12}-SO_2-R_{13}, -NR_{12}-SO_2-het, -C(O)H, -Z-NR_{12}-Z-O(C_1-C_6)alkyl, -Z-NR_{12}-Z-$NR_{12}R_{13}$, -Z-NR_{12}-(C_3-C_6)cycloalkyl, -Z-N(Z-O(C_1-C_6)alkyl)$_2$, -SO_2R_{12}, -SOR_{12}, -SR_{12}, -$SO_2NR_{12}R_{13}$, -O-C(O)-(C_1-C_4)alkyl, -O-SO_2-(C_1-C_4)alkyl, -halo or -CF_3;
Z for each occurrence is independently a) -(C_0-C_6)alkyl, b) -(C_2-C_6)alkenyl or c) -(C_2-C_6)alkynyl;
R_2 is a) -H, b) -halo, c) -OH, d) -(C_1-C_6)alkyl substituted with 0 or 1 -OH, e) -$NR_{12}R_{13}$, f) -Z-C(O)O(C_1-C_6)alkyl, g) -Z-C(O)$NR_{12}R_{13}$, h) -O-(C_1-C_6)alkyl, i) -Z-O-C(O)-(C_1-C_6)alkyl, j) -Z-O-(C_1-C_3)alkyl-C(O)-$NR_{12}R_{13}$, k) -Z-O-(C_1-C_3)alkyl-C(O)-O(C_1-C_6)alkyl, l) -O-(C_2-C_6)alkenyl, m) -O-(C_2-C_6)alkynyl, n) -O-Z-het, o) -COOH, p) -C(OH)$R_{12}R_{13}$ or q) -Z-CN;
R_3 is a) -H, b) -(C_1-C_{10})alkyl wherein 1 or 2 carbon atoms, other than the connecting carbon atom, may optionally be replaced with 1 or 2 heteroatoms independently selected from S, O and N and wherein each carbon atom is substituted with 0, 1 or 2 R_y, c) -(C_2-C_{10})alkenyl substituted with 0, 1 or 2 R_y, d) -(C_2-C_{10})alkynyl wherein 1 carbon atom, other than the connecting carbon atom, may optionally be replaced with 1 oxygen atom and wherein each carbon atom is substituted with 0, 1 or 2 R_y, e) -CH=C=CH_2, f) -CN, g) -(C_3-C_6)cycloalkyl, h) -Z-aryl, i) -Z-het, j) -C(O)O(C_1-C_6)alkyl, k) -O(C_1-C_6)alkyl, l) -Z-S-R_{12}, m) -Z-S(O)-R_{12}, n) -Z-S$(O)_2$-R_{12}, o) -CF_3 p) -NR_{12}O-(C_1-C_6)alkyl or q) -CH_2OR_y;
provided that one of R_2 and R_3 is absent when there is a double bond between CR_2R_3 (the 7 position) and the F moiety (the 8 position) of the C-ring;
Ry for each occurrence is independently a) -OH, b) -halo, c) -Z-CF_3, d) -Z-CF$(C_1-C_3$ alkyl$)_2$, e) -CN, f) -$NR_{12}R_{13}$, g) -(C_3-C_6)cycloalkyl, h) -(C_3-C_6)cycloalkenyl, i) -(C_0-C_3)alkyl-aryl, j) -het or k) -N_3;
or R_2 and R_3 are taken together to form a) =CHR_{11}, b) =NOR_{11}, c) =O, d) =N-NR_{12}, e) =N-NR_{12}-C(O)-R_{12}, f) oxiranyl or g) 1,3-dioxolan-4-yl;
R_4 and R_5 for each occurrence are independently a) -H, b) -CN, c) -(C_1-C_6)alkyl substituted with 0 to 3 halo, d) -(C_2-C_6)alkenyl substituted with 0 to 3 halo, e) -(C_2-C_6)alkynyl substituted with 0 to 3 halo, f) -O-(C_1-C_6) alkyl substituted with 0 to 3 halo, g) -O-(C_2-C_6)alkenyl substituted with 0 to 3 halo, h) -O-(C_2-C_6)alkynyl substituted with 0 to 3 halo, i) halo, j) -OH, k) (C_3-C_6)cycloalkyl or l) (C_3-C_6)cycloalkenyl;
or R_4 and R_5 are taken together to form =O;
R_6 is a) -H, b) -CN, c) -(C_1-C_6)alkyl substituted with 0 to 3 halo, d) -(C_2-C_6)alkenyl substituted with 0 to 3 halo, e) -(C_2-C_6)alkynyl substituted with 0 to 3 halo or f) -OH;
R_7 and R_{16} for each occurrence are independently a) -H, b) -halo, c) -CN, d) -(C_1-C_6)alkyl substituted with 0 to 3 halo, e) -(C_2-C_6)alkenyl substituted with 0 to 3 halo or f) -(C_2-C_6)alkynyl substituted with 0 to 3 halo; provided that R_7 is other than -CN or -halo when D is NR_7;
or R_7 and R_{16} are taken together to form =O;
R_8, R_9, R_{14} and R_{15} for each occurrence are independently a) -H, b) -halo, c) (C_1-C_6)alkyl substituted with 0 to 3 halo, d) -(C_2-C_6)alkenyl substituted with 0 to 3 halo, e) -(C_2-C_6)alkynyl substituted with 0 to 3 halo, f) -CN,

g) -(C_3-C_8)cycloalkyl, h) -(C_3-C_8)cycloalkenyl, i) -OH, j) -O-(C_1-C_8)alkyl, k) -O-(C_1-C_8)alkenyl, l) -O-(C_1-C_8)alkynyl, m) -$NR_{12}R_{13}$, n) -C(O)OR_{12} or o) -C(O)$NR_{12}R_{13}$;

or R_8 and R_9 are taken together on the C-ring to form =O; provided that when m is 2, only one set of R_8 and R_9 are taken together to form =O;

or R_{14} and R_{15} are taken together to form =O; provided that when R_{14} and R_{15} are taken together to form =O, D is other than CR_7 and E is other than C;

R_{10} is a) -(C_1-C_{10})alkyl substituted with 0 to 3 substituents independently selected from -halo, -OH and -N_3, b) -(C_2-C_{10})alkenyl substituted with 0 to 3 substituents independently selected from -halo, -OH and -N_3, c) -(C_2-C_{10})alkynyl substituted with 0 to 3 substituents independently selected from -halo, -OH and -N_3, d) -halo, e) -Z-CN, f) -OH, g) -Z-het, h) -Z-$NR_{12}R_{13}$, i) -Z-C(O)-het, j) -Z-C(O)-(C_1-C_8)alkyl, k) -Z-C(O)-$NR_{12}R_{13}$, l) -Z-C(O)-NR_{12}-Z-CN, m) -Z-C(O)-NR_{12}-Z-het, n) -Z-C(O)-NR_{12}-Z-aryl, o) -Z-C(O)-NR_{12}-Z-$NR_{12}R_{13}$, p) -Z-C(O)-NR_{12}-Z-O(C_1-C_8)alkyl, q) -(C_6-C_8)alkyl-C(O)OH, r) -Z-C(O)O(C_1-C_8)alkyl, s) -Z-O-(C_2-C_8)alkyl-het, t) -Z-O-(C_6-C_8)alkyl-aryl, u) -Z-O-(C_1-C_8)alkyl substituted with 0 to 2 R_x, v) -Z-O-(C_1-C_8)alkyl-CH(O), w) -Z-O-(C_1-C_8)alkyl-NR_{12}-het, x) -Z-O-Z-het-Z-het, y) -Z-O-Z-het-Z-$NR_{12}R_{13}$, z) -Z-O-Z-het-C(O)-het, a1) -Z-O-Z-C(O)-het, b1) -Z-O-Z-C(O)-het-het, c1) -Z-O-Z-C(O)-(C_1-C_8)alkyl, d1) -Z-O-Z-C(S)-$NR_{12}R_{13}$, e1) -Z-O-Z-C(O)-$NR_{12}R_{13}$, f1) -Z-O-Z-(C_1-C_2)alkyl-C(O)-$NR_{12}R_{13}$, g1) -Z-O-Z-C(O)-O(C_1-C_8)alkyl, h1) -Z-O-Z-C(O)-OH, i1) -Z-O-Z-C(O)-O-NR_{12}-O(C_1-C_8)alkyl, j1) -Z-O-Z-C(O)-NR_{12}-OH, k1) -Z-O-Z-C(O)-NR_{12}-Z-$NR_{12}R_{13}$, l1) -Z-O-Z-C(O)-NR_{12}-Z-het, m1) -Z-O-Z-C(O)-NR_{12}-SO_2-(C_1-C_8)alkyl, n1) -Z-O-Z-C(=NR_{13})($NR_{14}R_{15}$), o1) -Z-O-Z-C(=NOR_{12})($NR_{13}R_{14}$), p1) -Z-NR_{12}-C(O)-O-Z-$NR_{12}R_{13}$, q1) -Z-S-C(O)-$NR_{12}R_{13}$, r1) -Z-O-SO_2-(C_1-C_8)alkyl, s1) -Z-O-SO_2-aryl, t1) -Z-O-SO_2-$NR_{12}R_{13}$, u1) -Z-O-SO_2-CF_3, v1) -Z-NR_{12}C(O)OR_{13} or w1) -Z-NR_{12}C(O)R_{13};

or R_8 and R_{10} are taken together on the moiety of formula A-5 to form a) = O or b) = NOR_{12};

R_{11} is a) -H, b) -(C_1-C_8)alkyl, c) -(C_3-C_8)cycloalkyl or d) -(C_6-C_8)alkyl-aryl;

R_{12} and R_{13} for each occurrence are each independently a) -H, b) -(C_1-C_8)alkyl wherein 1 or 2 carbon atoms, other than the connecting carbon atom, may optionally be replaced with 1 or 2 heteroatoms independently selected from S, O and N and wherein each carbon atom is substituted with 0 to 6 halo, c) -(C_2-C_8)alkenyl substituted with 0 to 6 halo or d) -(C_1-C_8)alkynyl wherein 1 carbon atom, other than the connecting carbon atom, may optionally be replaced with 1 oxygen atom and wherein each carbon atom is substituted with 0 to 6 halo;

or R_{12} and R_{13} are taken together with N to form het;

or R_8 and R_{14} or R_{15} are taken together to form 1,3-dioxolanyl;

aryl is a) phenyl substituted with 0 to 3 R_x, b) naphthyl substituted with 0 to 3 R_x or c) biphenyl substituted with 0 to 3 R_x;

het is a 5-, 6- or 7-membered saturated, partially saturated or unsaturated ring containing from one (1) to three (3) heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another heterocycle; and the nitrogen may be in the oxidized state giving the N-oxide form; and substituted with 0 to 3 R_x;

R_x for each occurrence is independently a) -halo, b) -OH, c) -(C_1-C_8)alkyl, d) -(C_2-C_8)alkenyl, e) -(C_2-C_8)alkynyl, f) -O(C_1-C_8)alkyl, g) -O(C_2-C_8)alkenyl, h) -O(C_2-C_8)alkynyl, i) -(C_0-C_8)alkyl-$NR_{12}R_{13}$, j) -C(O)-$NR_{12}R_{13}$, k) -Z-SO_2R_{12}, l)-Z-SONR_{12}, m) -Z-SR_{12}, n) -NR_{12}-SO_2R_{13}, o) -NR_{12}-C(O)-R_{13}, p) -NR_{12}-OR_{13}, q) -SO_2-$NR_{12}R_{13}$, r) -CN, s) -CF_3, t) -C(O)(C_1-C_8)alkyl, u) =O, v) -Z-SO_2-phenyl or w) -Z-SO_2-het';

aryl' is phenyl, naphthyl or biphenyl;

het' is a 5-, 6- or 7-membered saturated, partially saturated or unsaturated ring containing from one (1) to three (3) heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another heterocycle; provided that:

1) X-R_1 is other than hydrogen or methyl;

2) when R_8 and R_{10} are substituents on the A-ring, they are other than mono- or di-methoxy;

3) when R_2 and R_3 are taken together to form =CHR_{11} or =O wherein R_{11} is -O(C_1-C_8)alkyl, then -X-R_1 is other than (C_1-C_4)alkyl;

4) when R_2 and R_3 taken together are C=O and R_8 is hydrogen on the A-ring; or when R_2 is hydroxy, R_3 is hydrogen and R_8 is hydrogen on the A-ring, then R_{10} is other than -O-(C_1-C_8)alkyl or -O-CH_2-phenyl at the 2-position of the A-ring;

5) when X-R_1 is (C_1-C_4)alkyl, (C_2-C_4)alkenyl or (C_2-C_4)alkynyl, R_9 and R_{10} are other than mono-hydroxy or =O, including the diol form thereof, when taken together; and

6) when X is absent, R_1 is other than a moiety containing a heteroatom independently selected from N, O or S directly attached to the juncture of the B-ring and the C-ring.

18. The use of claim 17 wherein the glucocorticoid receptor antagonist is a compound selected from the group consisting of:

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-(4-pyridinylmethyl)-, [4bS-(4bα, 7α, 8aβ)]-;
2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-(2-pyridinylmethyl)-, [4bS-(4bα,7α,8aβ)]-;
2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-(3-pyridinylmethyl)-, [4bS-(4bα,7α,8aβ)]-;
carbamic acid, [2-(dimethylamino)ethyl]-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl ester,[4bS-(4bα,7α,8aβ)]-;
2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-pyrazinyl-, [4bS-(4bα,7α,8aβ)]-;
2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-(4-pyridinylmethoxy)-, [2R-(2α,4aα,10aβ)];
2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-(2-pyridinylmethoxy)-, [2R-(2α,4aα,10aβ)];
2-phenanthrenecarbonitrile, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-, [4bS-(4bα,7α,8aβ)]-;
2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-(1-propynyl)-, [4bS-(4bα,7α,8aβ)]-;
2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-propyl-, [4bS-(4bα,7α,8aβ)]-;
2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-N-(2-pyridinylmethyl)-, [4bS-(4bα,7α,8aβ)]-;
2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(3-pyridinylmethoxy)-2-(3,3,3-trifluoropropyl)-, [2S-(2α,4aα,10aβ)]-;
2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-3-pyridinyl)methoxy]-4a-(phenylmethyl)-2-(3,3,3-trifluoropropyl)-,[2S-(2α,4aα,10aβ)]-;
2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-(3,3,3-trifluoropropyl)-, (4bS,7S,8aR);
2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-methyl-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-, (4bS,7R,8aR)-;
2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-methyl-4b-(phenylmethyl)-N-3-pyridinyl-, (4bS,7R,8aR)-;
2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-3-pyridinyl)methoxy]-4a-(phenylmethyl)-2-(trifluoromethyl)-, (2R,4aS, 10aR)-; and
2-phenanthrenecarboxamide, 4b, 5, 6, 7, 8, 8a, 9, 10-octahydro-7-hydroxy-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-(trifluoromethyl)-, (4bS, 7R, 8aR)-.

19. A pharmaceutical composition which comprises a corticotropin releasing factor antagonist and a pharmaceutically acceptable vehicle, carrier or diluent.

20. The composition of claim 19 which comprises a therapeutically effective amount of a corticotropin releasing factor antagonist.

21. The compositon of claim 20 wherein the corticoptropin releasing factor antagonist is a compound selected from the group consisting of the compounds defined in claim 14.

22. The composition of claim 20 wherein the corticotropin releasing factor antagonist is a compound selected from the group consisting of the compounds defined in claim 15.

23. The composition of claim 19 which further comprises an amount of a glucocoticoid receptor antagonist and a pharmaceutically acceptable vehicle, carrier or diluent.

24. The composition of claim 23 wherein the glucocorticoid receptor antagonist is a compound defined in claim 17.

25. The composition of claim 24 wherein the glucocorticoid receptor antagonist is a compond selected from the group

consisting of compounds defined in claim 18.